A macrolide might once again be available for empiric oral treatment of severe CAP, Dr. Carlos Barrera said.

MONTREAL – A new, next-generation macrolide, solithromycin, showed safety and efficacy as a once-daily oral agent that was noninferior to the comparator oral antibiotic, the fluoroquinolone moxifloxacin, in a phase III trial.

Macrolide resistance among strains of Streptococcus pneumoniae that cause many U.S. cases of severe community-acquired pneumonia has become common, complicating treatment of this common infection with a macrolide, Dr. Carlos M. Barrera explained at the annual meeting of the American College of Chest Physicians.


The high-flow nasal cannula largely replaced noninvasive ventilation in our CCU patients with no change in escalation rates or mortality. The high-flow nasal cannula should be considered a first-line treatment in this setting,” said Dr. Troy S. Browne at the annual meeting of the American College of Chest Physicians.

He and his associates at Tauranga (New Zealand) Hospital compared their experience using standard noninvasive ventilation on 249 CCU patients who needed respiratory support during May-November 2012 with 248 patients who received ventilation with a high-flow nasal cannula once it became the default strategy in the coronary care unit.

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Catheter-directed thrombolysis surpassed systemic thrombolysis for minimizing in-hospital mortality of patients with an acute pulmonary embolism in a review of more than 1,500 U.S. patients. The review also found evidence that U.S. pulmonary embolism (PE) patients increasingly undergo catheter-directed thrombolysis, with usage jumping by more than 50% from 2010 to 2012, although in 2012 U.S. clinicians performed catheter-directed thrombolysis on 160 patients with an acute pulmonary embolism (PE) who were included in a national U.S. registry of hospitalized patients, Dr. Amina Saqib said at the annual meeting of the American College of Chest Physicians.

Catheter-directed thrombolysis resulted in a 9% in-hospital mortality rate and a 10% combined rate.
OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids.

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.

- Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
- Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase type 5; SC: subcutaneous; SERAPHIN: Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; ULN: upper limit of normal; WHO: World Health Organization.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
SERAPHIN: The first long-term outcome trial in PAH (average treatment 2 years) to demonstrate the use of both monotherapy and combination therapy to delay disease progression\(^1\)\(^2\)

**Patients were treated with OPSUMIT monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids\(^3\)**
- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients\(^3\)
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years\(^3\)
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study\(^3\)

SERAPHIN was a randomized, double-blind, placebo-controlled, event-driven outcome study to assess the effect of OPSUMIT on disease progression (time to first significant morbidity or mortality event), as defined by death, atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).\(^1\)\(^2\)

**WARNINGS AND PRECAUTIONS (continued)**

**Hepatotoxicity**
- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN was 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

*Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.*
WARNINGS AND PRECAUTIONS (continued)

Hemoglobin Decrease
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
INDICATION (continued)
Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids.[1]

Subgroup analysis of the primary endpoint in the SERAPHIN study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>OPSUMIT No. of events/No. of patients</th>
<th>Placebo No. of events/No. of patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment effect</td>
<td>0.55 (0.41, 0.73)</td>
<td>76/242</td>
<td>116/250</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant PAH therapy at baseline</td>
<td>0.62 (0.43, 0.89)</td>
<td>50/154</td>
<td>68/154</td>
<td>0.45 (0.28, 0.72)</td>
</tr>
<tr>
<td>Combination with PDE-5 inhibitors and/or inhaled or oral prostanoids†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td>26/88</td>
<td>48/96</td>
<td></td>
</tr>
</tbody>
</table>

†The OPSUMIT indication includes combination with phosphodiesterase-5 inhibitors or inhaled prostanoids, but not oral prostanoids.

In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)... Don’t delay, treat today—keep disease progression in mind from the start of therapy in FC II and III patients.
OPSUMIT is approved for use as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

ADVERSE REACTIONS
- Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS
- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

CI: confidence interval; CYP: cytochrome P450; FC: functional class; HIV: human immunodeficiency virus.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

**BRIEF SUMMARY**

The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing.

**WARNING: EMBRYO-FETAL TOXICITY**

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see Contraindications (Pregnancy), Warnings and Precautions (Embry-fetal Toxicity), Use in Specific Populations (Pregnancy)].
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception [see Use in Special Populations (Females and Males of Reproductive Potential)].
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (OPSUMIT REMS Program)].

**INDICATIONS AND USAGE**

**Pulmonary Arterial Hypertension**

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

**OPSUMIT REMS Program**

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)].

**CONTRAINDICATIONS**

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see Warnings and Precautions (Embryo-fetal Toxicity) and Use in Specific Populations (Pregnancy)].

**WARNINGS AND PRECAUTIONS**

**Embryo-fetal Toxicity**

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy; ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see Dosage and Administration section 2.2 in full Prescribing Information and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)].

**OPSUMIT REMS Program**

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

**Adverse Reactions (Clinical Trial Experience)**

- Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 × ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;8 × ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated. Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

**Hemoglobin Decrease**

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see Adverse Reactions (Clinical Trial Experience)].

**Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)**

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

**Decreased Sperm Counts**

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

**ADVERSE REACTIONS**

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see Warnings and Precautions (Embryo-fetal Toxicity)]
- Hepatotoxicity [see Warnings and Precautions (Hepatotoxicity)]
- Decrease in Hemoglobin [see Warnings and Precautions (Hemoglobin Decrease)]

**Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of OPSUMIT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Immune system disorders:** hypersensitivity reactions (angioedema, pruritus and rash)

**Respiratory, thoracic and mediastinal disorders:** nasal congestion
DRUG INTERACTIONS

OPSUMIT® (macitentan)

Strong CYP3A4 Inhibitors

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetics)].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors (see Clinical Pharmacology (Pharmacokinetics)). Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications (Pregnancy)].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine device (IUD), contraceptive implants or tubal sterilization) or a combination of devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a device is chosen, the chosen method of contraception must be continued until the patient is certain that pregnancy cannot occur.

Male

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Counts) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

OVERDOSE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

Drug Interactions

In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1

Interacting drug

Macitentan

Active metabolite

Sildenafil

Ketoconazole

Rifampin

Cyclosporine

Effect of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats. Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected. Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans. There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

Manufactured for:

Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA

ACT20150219


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Novel Macrolide for Pneumonia

Solithromycin from page 1

Dr. Vera A. DePalo, MBA, FCCP

Physician

CHEST

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Dr. Barbara Phillips is the new President of the College. • 64

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Dr. Vera A. DePalo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

In This Issue

November 2015 • CHEST PHYSICIAN

Novel Macrolide for Pneumonia

The data make solithromycin look like a promising way to once again have a macrolide available for empirical oral treatment of moderate-severe community-acquired pneumonia, but you can’t do that anymore,” Dr. Muthiah said in an interview.

Several patients enrolled in each of the two arms of the study.

The study’s primary endpoint for Food and Drug Administration approval of solithromycin was early clinical response, defined as an improvement in at least two listed symptoms at 72 hours after onset of treatment.

That endpoint occurred in 78% of patients enrolled in each of the two arms of the study.

The safety results, however, showed that solithromycin produced a higher number of patients with a liver-enzyme elevation, compared with patients treated with moxifloxacin.

In SOLITAIRE-IV, Cempra reported that grade 5 increase in levels of alanine transaminase (ALT) occurred in 8% of patients on solithromycin and in 3% of patients on moxifloxacin.

Grade 4 increases in ALT occurred in less than 1% of patients in both treatment arms.

In the current, orally administered trial, grade 3 ALT increases occurred in 5% of patients treated with solithromycin and in 2% of patients treated with moxifloxacin.

It is always important to remember that the antibiotic can be a very useful tool in understanding the local resistance pattern of microbes and to guide antimicrobial selection.
Better-tolerated ventilation

High-flow cannula from page 1

cannula produced similar outcomes while being ‘better tolerated and less of a burden for the nursing staff to manage,’ said Dr. Browne, who is an anesthesiology and critical care medicine specialist at the Tauranga Hospital.

A key feature of the high-flow nasal cannula system is the warmed and humidified mix of oxygen and air that it pumps.

“If you run a nasal cannula without this, you dry out the patient’s nose at 5 or 6 L/min, and it’s very uncomfortable. But I’ve worn a high-flow nasal cannula with 30 L/min flow and I couldn’t tell I was wearing it,” commented Dr. Thomas Fuhrman, FCCP, chief of anesthesiology at the Bay Pines (Fla.) VA Healthcare System.

“It’s high enough flow to open the lungs but much better tolerated” than standard noninvasive ventilation, Dr. Fuhrman said in an interview.

Patients can open their mouths, swallow, and eat while wearing the high-flow nasal cannula, he noted.

“This report is a step forward and will help spur adoption” of the high-flow nasal cannula, Dr. Fuhrman predicted. Many cardiologists are not yet aware of it as it’s usually placed by intensivists. Over time, additional indications for the device will develop, he added.

The specific system used in Tauranga Hospital’s coronary care unit is the Optiflow high-flow nasal cannula along with the Airvo pumping system, both marketed by Fisher & Paykel Healthcare. During the 6 months preceding November 2012, 107 of 249 (43%) CCU patients underwent noninvasive ventilation during the first 40 hours following CCU admission. During the subsequent period ventilation started on 67 of 248 (27%) during the first 40 hours. Of those, 60 (90%) received sufficient treatment with a high-flow nasal cannula, while 7 (10%) required standard noninvasive ventilation.

Patient outcomes during the two study periods were similar.

A more definitive comparison of noninvasive ventilation and high-flow nasal cannula treatment requires a prospective, randomized study, Dr. Browne said.

Reduced mortality, higher cost

Catheter-directed thrombolysis from page 1

of in-hospital mortality plus intracerebral hemorrhages, rates significantly below those tallied in propensity score–matched patients who underwent systemic thrombolysis of their acute PE.

The matched group with systemic thrombolysis had a 17% in-hospital mortality rate and a 17% combined mortality plus intracerebral hemorrhage rate, said Dr. Saqib, a researcher at Staten Island University Hospital.

“To the best of our knowledge, this is the first, large, nationwide, observational study that compared safety and efficacy outcomes between systemic thrombolysis and catheter-directed thrombolysis in acute PE,” Dr. Saqib said.

The U.S. data, collected during 2010-2012, also showed that, after adjustment for clinical and demographic variables, each acute PE treatment by catheter-directed thrombolysis cost an average $9,428 more than systemic thrombolysis, she said.

“We need to more systematically identify the patients with an acute PE who could benefit from catheter-directed thrombolysis, especially patients with a massive PE,” commented Dr. Muthiah P. Muthiah, FCCP, a critical-care medicine physician at the University of Tennessee Health Science Center in Memphis. “This may be something to offer to patients who have an absolute contraindication for systemic thrombolysis, such as recent surgery, but it is not available everywhere,” Dr. Muthiah said in an interview.

Dr. Saqib and her associates used data collected by the Federal National Inpatient Sample. Among U.S. patients hospitalized during 2010-2012 and entered into this database, they identified 1,169 adult acute PE patients who underwent systemic thrombolysis and 352 patients who received catheter-directed thrombolysis. The patients averaged about 58 years old and just under half were men.

The propensity score–adjusted analysis also showed no statistically significant difference between the two treatment approaches for the incidence of intracerebral hemorrhage, any hemorrhages requiring a transfusion, new-onset acute renal failure, or hospital length of stay.

Among the patients treated by catheter-directed thrombolysis, all the intracerebral hemorrhages occurred during 2010; during 2011 and 2012 none of the patients treated this way had an intracerebral hemorrhage, Dr. Saqib noted.

Although the findings were consistent with results from prior analyses, the propensity-score adjustment used in the current study cannot fully account for all unmeasured confounding factors.

The best way to compare catheter-directed thrombolysis and systemic thrombolysis for treating acute PE would be in a prospective, randomized study, Dr. Saqib said.

Dr. Saqib and Dr. Muthiah had no relevant financial disclosures.
Radiation dose exceeds 50 mSv in 2% of ICU patients

BY MITCHEL L. ZOLER
Frontline Medical News

MONTREAL – Some of the sickest patients treated at U.S. hospitals receive high levels of radiation exposure, based on a review of more than 4,000 medical ICU patients treated recently at one U.S. quaternary-care center.

During 2013, 98 patients admitted to the medical ICU at the Cleveland Clinic – 2% of the 4,155 patients who passed through the medical ICU that year – had cumulative radiation exposure of at least 50 mSv while in the ICU, thereby exceeding the U.S. standard for maximum annual workplace exposure, Dr. Sudhir Krishnan said at the annual meeting of the American College of Chest Physicians. The finding raises questions of whether all these exposures are appropriate and whether they reflect overuse of certain imaging modalities.

Dr. Krishnan and his associates ran a retrospective review of case records for the medical ICU–admitted patients at the Cleveland Clinic during 2013 (Chest. 2015 Oct 25. doi: 10.1378/chest.2278486). During their ICU stay, 3,940 patients (84%) received some amount of radiation exposure. Exposure averaged 7 mSv, with a median of 1.5 mSv. The radiation exposure came primarily from imaging and more specifically from CT examinations, which produced more than half of all radiation-exposure episodes. Other sources included x-rays, nuclear scans, and interventional procedures.

Based on typical radiation dosages received during each type of procedure, the researchers calculated an estimated total radiation dosage received by each patient during their ICU stay. Nearly two-thirds of patients had an exposure of less than 3 mSv; the average annual exposure a person receives from ambient radiation. A quarter of the patients had an exposure of 3-14 mSv; 11% had an exposure of 15-49 mSv; and 2% – 98 patients – had exposure during their ICU stay that ran to 50 mSv or greater, exceeding the U.S. workplace annual maximum. Thirteen patients had an exposure level during their ICU stay that reached 100 mSv or higher; the maximum exposure level was in a patient with cumulative exposure of 176 mSv, said Dr. Krishnan, a critical-care medicine specialist at the Cleveland Clinic.

He and his coworkers did a multivariate analysis to identify factors that linked with a higher likelihood of having high radiation exposure. Patients at greatest risk for high exposure levels were sicker patients with higher APACHE 3 scores, longer stays in the ICU, and the presence of cirrhosis, but those most at risk also tended to be younger.

Rates of both ICU deaths and deaths during the entire hospitalization were significantly higher among those with radiation exposure that was 50 mSv or greater.

Dr. Krishnan cautioned that he has not run any analysis that assessed the appropriateness of the imaging that the ICU patients received, nor did he have any data documenting the clinical consequences to the patients who had higher radiation exposure. Despite that uncertainty, he suggested that efforts focus on avoiding unnecessary radiation exposure to patients.

Hypothermia after nonshockable-rhythm cardiac arrest

BY MARY ANN MOON
Frontline Medical News

Therapeutic hypothermia significantly raises the rate of survival with a good neurologic outcome among patients who are comatose after a cardiac arrest with a nonshockable initial rhythm, according to a report published online in Circulation.

Many observational and retrospective cohort studies have examined the possible benefits of therapeutic hypothermia in this patient population, but they have produced conflicting results. No prospective randomized clinical trials have been published as yet. This has led to controversy. Some clinicians insist the treatment should be reserved only for patients who meet the narrow criteria for which there is good supportive evidence; others, eager for any clinical strategy that can improve the outcomes of these critically ill patients, routinely expand its use to comatose patients regardless of their initial heart rhythm or the location of the cardiac arrest, wrote Dr. Sarah M. Perman of the department of emergency medicine, University of Colorado, Aurora, and her associates.

They studied the issue using data from a national registry of patients treated at 16 medical centers that sometimes use therapeutic hypothermia after cardiac arrest. The researchers assessed the records of 519 adults during a 3-year period who had a nontraumatic cardiac arrest and initially registered either pulseless electrical activity or asystole, then had a return of spontaneous circulation but remained comatose.

Approximately half of these comatose survivors (262 patients) were treated with therapeutic hypothermia according to their hospital’s usual protocols, and the other half (257 control subjects) received standard care without therapeutic hypothermia.

Patients who received the intervention were significantly younger (62 vs 69 years), had a longer duration of cardiac arrest (23 vs 13 minutes), had a higher incidence of asystole as their primary cardiac rhythm (45% vs 35%), and were much more likely to have an out-of-hospital cardiac arrest (82% vs 39%).

To account for these marked differences and to control for confounding by indication, the investigators used propensity matching and identified 200 matched pairs of patients.

In the propensity-matched cohort, the rate of survival to hospital discharge was significantly higher with therapeutic hypothermia (29%) than without it (15%), as was the rate of survival with a favorable neurologic outcome (21% vs 10%). And in a multivariate analysis of factors contributing to positive patient outcomes, the intervention was associated with a 3.5-fold increase in favorable neurologic outcomes. A further analysis of the data showed that therapeutic hypothermia was associated with improved survival, with an OR of 2.8.

In addition, an analysis of outcomes across various subgroups of patients showed that regardless of the location of their cardiac arrest, patients were consistently more likely to survive to hospital discharge neurologically intact if they received therapeutic hypothermia (OR, 2.1 for out-of-hospital and OR, 4.2 for in-hospital cardiac arrest).

“These results lend support to a broadening of indications for therapeutic hypothermia in comatose post-arrest patients with initial nonshockable rhythms,” Dr. Perman and her associates said.
New guidelines on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) set upper limits on chest compression rate and depth, add naloxone to the care of suspected opioid abusers, and remove vasopressin from the advanced cardiac life support (ACLS) algorithm.

The American Heart Association published its revised guidelines in Circulation. The AHA released its previous guidelines in 2010.

“Everyone has a role to play in the chain of survival – from bystanders to dispatchers, emergency responders to health care providers,” Dr. Mark Creager said in a statement.

“When everyone knows their role, knows CPR, and works together, we can dramatically improve cardiac arrest victims’ chances of survival,” said Dr. Creager, AHA president and director of the Heart and Vascular Center at Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

The 2015 guidelines’ new recommendations include the following:

- **Resuscitation pathways.** The guidelines note that the resuscitation pathways are very different for patients who experience cardiac arrest present in a hospital setting (IHCA) as compared to an out-of-hospital setting (OHCA). In OHCA, the patient depends on lay rescuers to not only recognize the situation but also call for help, initiate CPR, and, if available, administer defibrillation until emergency medical personnel arrive. However, IHCA involves prevention of cardiac arrest and smooth delivery of care in a multidisciplinary setting.

- **Layperson CPR.** Untrained lay rescuers should provide compression-only CPR for OHCA. Trained lay rescuers who are able to provide rescue breaths should begin CPR with compressions followed by breaths at a ratio of 30 compressions to two breaths. Compression-only CPR is easier to perform for untrained lay rescuers, the guidelines note, and survival rates are similar using CPR with or without rescue breaths in adult cardiac arrest with a cardiac etiology.

- **Compression rate and depth.** The guidelines set upper limits on chest compression depth and heart rate, recommending a compression rate of 100-120 compressions per minute with a depth of at least 2 inches, not to exceed 2.4 inches in adults.

- **Social media dispatching.** Despite limited evidence, the authors said that it may be reasonable for communities to use social media technologies to alert lay rescuers with mobile phones about nearby OHCA cases.

- **Naloxone and opioid addiction.** Also new is the recommended use of naloxone for patients with suspected or known opioid addiction by appropriately trained lay rescuers or basic life support (BLS) providers.

- **CPR training.** The guidelines highlight several changes to simplify health care provider training in CPR. For example, trained rescuers can simultaneously perform some tasks.
COPD treatment built on strong roots
STIOLTO™ RESPIMAT®

INDICATION
Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray is a combination of tiotropium, an anticholinergic, and olodaterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use
STIOLTO is NOT indicated to treat acute deterioration of COPD and is not indicated to treat asthma.

IMPORTANT SAFETY INFORMATION
WARNING: ASTHMA-RELATED DEATH
Long-acting beta2-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma.

CONTRAINDICATION
All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. STIOLTO is contraindicated in patients with hypersensitivity to tiotropium, ipratropium (atropine derivatives), olodaterol, or any component of this product.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO.

WARNINGS AND PRECAUTIONS
STIOLTO should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition, or used as rescue therapy for acute symptoms. Acute symptoms should be treated with an inhaled short-acting beta2-agonist. Patients who have been taking inhaled, short-acting beta2-agonists on a regular basis should discontinue the regular use of these drugs and use them only for acute respiratory symptoms.

STIOLTO should not be used more often or at higher doses than recommended, or in conjunction with other LABA as an overdose may result.

Immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO. If such a reaction occurs, discontinue therapy with STIOLTO and consider alternative treatments. Patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO.

If paradoxical bronchospasm occurs, STIOLTO should be discontinued immediately.

STIOLTO can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STIOLTO may need to be discontinued. Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.
Finally, the guidelines highlight updates in post–cardiac arrest care, including a wider range of target temperatures, between 32°C and 36°C, to be maintained for at least 24 hours in comatose adults with ROSC after cardiac arrest.

In comparison, the 2010 guidelines called for a target temperature range of 32°C to 34°C for 12-24 hours. The guidelines also detail new updates for acute coronary syndrome, pediatric BLS, pediatric ACLS, and neonatal resuscitation.

As the AHA updates its CPR guidelines, it’s also important for lay rescuers and health providers to update their own training, noted Dr. Clifton Callaway, chair of the AHA’s Emergency Cardiovascular Care (ECC) committee.

“Research shows resuscitation skills can decline within a few months after training — far before the 2-year period in which basic and advanced life support skills are currently evaluated,” cautioned Dr. Callaway, professor of emergency medicine at the University of Pittsburgh.

“Frequent training with shorter intervals of basic and advanced cardiovascular life support skills may be helpful for providers who are likely to encounter a cardiac arrest to ensure the patient receives high-quality CPR,” he added.

Introducing STIOLTO™ RESPIMAT®: from the makers of SPIRIVA®

- Significant improvement in lung function vs SPIRIVA® RESPIMAT® and olodaterol
- Lung function improvement starting within 5 minutes and lasting 24 hours
- STIOLTO RESPIMAT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- Improved lung function vs SPIRIVA RESPIMAT earlier in the course of COPD
- Reduced rescue medication use at week 52
- Frequency of adverse events in patients taking STIOLTO RESPIMAT was comparable to that for patients taking the individual components

Help your patients improve lung function from the start of COPD maintenance therapy with STIOLTO RESPIMAT

*FEV₁, forced expiratory volume in 1 second.

IMPORTANT SAFETY INFORMATION (CONT’D)

Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Use with caution in patients with urinary retention, which can be associated with symptoms like difficulty passing urine and painful urination in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment or symptoms develop. Use with caution in patients with urinary retention, which can be associated with symptoms like difficulty passing urine and painful urination in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment or symptoms develop. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Use with caution in patients with urinary retention, which can be associated with symptoms like difficulty passing urine and painful urination in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment or symptoms develop. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.

- Avoid co-administration of STIOLTO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

STIOLTO is for oral inhalation only. The STIOLTO cartridge is only intended for use with the STIOLTO RESPIMAT inhaler. Inform patients not to spray STIOLTO into the eyes.

No pull-out pneumothorax with ‘party balloon Valsalva’

BY M. ALEXANDER OTTO
Frontline Medical News

CHICAGO – Investigators have come up with a simple way to reduce and maybe even eliminate pull-out pneumothoraces during chest tube removal.

Instead of standard inhale or exhale Valsalva maneuvers, they have their patients blow a party balloon as the tube is pulled.

That produces the same Valsalva effects as the standard maneuvers, but with two significant advantages. First, it’s easy to explain and for patients to understand and do – not much more instruction is required than “blow up the balloon” – and, secondly, the inflating balloon is a visual check to make sure patients are doing the maneuver correctly. “It’s easy to see,” said lead investigator Dr. Puwadon Thitivara-

STIOLTO™ RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray, for oral inhalation use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta-2-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta-adrenergic agonist (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with exacerbations that have been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma (see Contraindications, Warnings and Precautions).

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STIOLTO RESPIMAT is a combination of tiotropium and olodaterol indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Uncontrolled obstructive symptoms, including chronic bronchitis and/or emphysema, may be considered indications for treatment with STIOLTO RESPIMAT. STIOLTO RESPIMAT is not indicated for the treatment of asthma (see Contraindications, Warnings and Precautions).

CONTRAINDICATIONS: All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication (see Warnings and Precautions). STIOLTO RESPIMAT is not indicated for the treatment of asthma. The safety and effectiveness of STIOLTO RESPIMAT in asthma have not been established.

WARNINGS AND PRECAUTIONS: Asthma-Related Death (See Warnings and Precautions)

Data from a large, placebo-controlled trial in asthmatic patients showed that long-acting beta-2-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta-2-adrenergic agonists. A 28-week, placebo-controlled US study comparing the safety of another long-acting beta-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/17,176 in patients treated with salmeterol vs. 3/17,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta-2-adrenergic agonists, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STIOLTO RESPIMAT has been conducted. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma (see Contraindications, Warnings and Precautions).

Deterioration of Disease and Acute Episodes: STIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STIOLTO RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STIOLTO RESPIMAT in this setting is inappropriate. STIOLTO RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STIOLTO RESPIMAT has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta-agonist. When beginning STIOLTO RESPIMAT, patients who have been withdrawn from inhaled, short-acting beta-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing STIOLTO RESPIMAT, the healthcare provider should also prescribe a short-acting beta-agonist and instruct the patient on how it should be used. Inhaled beta-agonist use is a signal of deteriorating disease. High-intensity, prompt medical attention should be given. If tolerated, the inhaled beta-agonist should be used on an as needed (PRN) basis. If the patient requires more than two short-acting beta-agonists daily or more than six applications of a metered-dose inhaler in one month, the patient should be withdrawn from the inhaled beta-agonist and closely monitored for deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the dosage of STIOLTO RESPIMAT beyond the recommended dose is inappropriate in this situation. Excessive Use of STIOLTO RESPIMAT and Use With Other Long-Acting Beta-Agonists: As with other inhaled drugs containing beta-2-agonists, STIOLTO RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta-2-agonists as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Inhaled beta-2-agonists, such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. STIOLTO RESPIMAT is not indicated for the treatment of asthma (see Contraindications, Warnings and Precautions).

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), flushing, or rash have been reported. Hypokalemia, if occurring, has also been reported in clinical trials with STIOLTO RESPIMAT.

ADVERSE REACTIONS: LABA, such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. STIOLTO RESPIMAT is not indicated for the treatment of asthma (see Contraindications, Warnings and Precautions). The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see Warnings and Precautions]. Paradoxical bronchospasm [see Warnings and Precautions]. Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: Because clinical trials are conducted under widely varying conditions, the frequency of adverse reactions observed in the clinical trials of a drug cannot be compared to the incidence of reactions in the clinical trials of another drug and may not reflect the incidence of reactions observed in practice. The clinical program for STIOLTO RESPIMAT included 7151 subjects with COPD in two 52-week active-controlled trials, one 12-week placebo-controlled trial, three 6-week placebo-controlled cross-over trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1 dose of STIOLTO RESPIMAT. Adverse reactions observed in the 52-week studies were consistent with those observed in the 52-week trials, which formed the primary safety database. The primary safety database consisted of pooled data from the 52-week double-blind, active-controlled, parallel group confirmatory clinical trials. These trials included 5182 adult COPD patients (72.9% males and 27.1% females) 40 years of age and older. Of these patients, 1029 were treated with STIOLTO RESPIMAT once daily. The STIOLTO RESPIMAT group was composed of mostly Caucasians (71.1%) with a mean age of 63.8 years and a mean percent predicted FEV1, at baseline of 43.2%. In these two trials, tiotropium 18 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used. In these two clinical trials, 14% of patients exposed to STIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 18 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for STIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 18 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation and pneumonia. Table 1 shows all adverse drug reactions that occurred with an incidence of >3% in the STIOLTO RESPIMAT treatment group and a higher incidence rate than the active comparator groups listed.

STIOLTO RESPIMAT. No study adequate to determine embodiment of acute exacerbations. In these two trials, tiotropium 18 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used. In these two clinical trials, 14% of patients exposed to STIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 18 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for STIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 18 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation and pneumonia.
Table 1: Number and frequency of adverse drug reactions greater than 2% and higher than any of the comparators for tiotropium and/or olodaterol in COPD patients exposed to STIOLTO RESPIMAT. Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older

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<td>45 (4.4)</td>
<td>31 (3.0)</td>
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<tr>
<td>Olodaterol</td>
<td>40 (3.9)</td>
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<td>Back Pain</td>
<td>37 (3.6)</td>
<td>19 (1.8)</td>
<td>35 (3.3)</td>
</tr>
</tbody>
</table>

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in 2% of patients in clinical studies and with no further information available are listed below:

- Skin and subcutaneous disorders: rash, pruritus, urticaria, eczema, dermatitis, angioedema, urticaria, skin infection, skin ulcer, dry skin, skin hyperhidrosis (including immediate reactions); Musculoskeletal and connective tissue disorders: arthralgia, joint swelling.

In a drug interaction study using the inspiratory cuff and PEEP and inspiratory balloon technique, a 7.2-fold increase of olodaterol maximum plasma concentrations and AUC was observed (see Pharmacokinetics). Olodaterol was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment of STIOLTO RESPIMAT is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with STIOLTO RESPIMAT or its individual components, tiotropium bromide and olodaterol, in pregnant women. Animal reproduction studies were conducted with the individual components of STIOLTO RESPIMAT, tiotropium bromide and olodaterol. STIOLTO RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

STIOLTO RESPIMAT: No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 95 times the recommended human daily inhalation dose (RHID, on a mcg/m² basis at a maternal inhalation dose of 141 mcg/kg/day). In rodents, olodaterol caused fetal body weight loss and 95% of the RHID (on a mcg/m² basis at maternal inhalation doses of 9 mg/kg/day and rabbits, respectively). Olodaterol was not teratogenic in rats and rabbits at approximately 2731 RHID on the AUC basis at a maternal inhalation dose of 1054 mcg/kg/day). Placental transfer of olodaterol was observed in pregnant rats. Olodaterol has not been shown to be teratogenic in New Zealand rabbits at approximately 7130 times the RHID in adults (on an AUC basis at a maternal inhalation dose of 2469 mcg/kg/day). Olodaterol exhibited the following fetal toxicities: enlarged or small heart, extraossa, abnormalities, and split or distal sternal sternum. Significant effects occurred at approximately 1535 times the RHID in adults (on an AUC basis at a maternal inhalation dose of 974 mcg/kg/day).

Labor and Delivery: There are no adequate and well-controlled human studies with STIOLTO RESPIMAT that have investigated the effects of STIOLTO RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractions, use of STIOLTO RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Clinical data from nursing women or infants exposed to STIOLTO RESPIMAT or its individual active components are not available. Tiotropium, olodaterol, and metabolites of olodaterol are excreted into the milk of lactating rats. It is not known whether these compounds are excreted in human milk, but because many drugs are excreted in human milk and given these findings, caution should be exercised if STIOLTO RESPIMAT is administered to a nursing woman. Pediatric Use: COPD does not normally occur in children. The safety and efficacy of STIOLTO RESPIMAT in the pediatric population has not been established.

Geriatric Use: Based on available data, no adjustment of STIOLTO RESPIMAT dosage in geriatric patients is warranted. Of the 1029 patients who received STIOLTO RESPIMAT, the recommended dose once daily in the clinical studies from the pooled 1-year database, 523 (51.0%) were ≤65 years of age, 282 (27.2%) were 65 to <75, 96 (9.3%) were 75 to <85, and 1 (0.1%) was ≥85. No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall.

Hepatic Impairment: No dose adjustment is needed for patients with mild and moderate hepatic impairment.

In studies in subjects with severe hepatic impairment was not performed. Renal Impairment: No dose adjustment of Precautions and Adverse is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of 15 to 50 mL/min) treated with STIOLTO RESPIMAT should be monitored carefully for anticholinergic side effects (see Warnings and Precautions).

OVERDOSAGE: STIOLTO RESPIMAT contains both tiotropium bromide and olodaterol; therefore, the risks associated with overdosage for the individual components described below apply to STIOLTO RESPIMAT. Tiotropium: High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects after a single inhalation dose of up to 252 mcg tiotropium in healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctival injection and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following observed of up to 40 mcg tiotropium bromide with a median solution in healthy subjects. Expected signs and symptoms with overdosage of olodaterol are those of excessive beta-agonist stimulation and are likely to be systemic side effects. Cardiovascular and cardiac arrest and death may be associated with an overdose of olodaterol. Treatment of these symptoms involves discontinuation of STIOLTO RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of STIOLTO RESPIMAT. Cardiac monitoring is recommended in cases of overdose.

Inflating a balloon during tube removal may trap standard valvula.

close in a group comparison of standard patients with balloon patients (P = .11). The investigators estimated they would need almost 600 hundred subjects to reach statistical significance.

Even so, the party balloon technique appears to be “easier and safer” than standard maneuvers, as well as “reproducible and cheap, and it can prevent recurrent pneumothorax. It can be used as an alternative to the classic valvula,” said Dr. Thitivara-porn, a cardiothoracic surgery resident at the Bangkok hospital.

The balloon method is being used there now in nontrauma patients, as well, but the standard maneuvers are also being used until the balloon technique shows statistically significant benefits, he said.

With manometry, the team found that a party balloon’s internal pressure builds quickly as it’s inflated from a starting diameter of about 4.5 cm to about 9 cm, peaking at about 60 mm Hg; pressure trails off to about 40 mm Hg as inflation continues past 9 cm.

The investigators have no relevant disclosures.

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Utilization management programs may be needed to address policy change.

Resource allocation may be influenced by a number of personal, community, or society values. Consequently, the result of the previously described conflict is variation of patient care. Practice variation has been characterized as one of the most common reasons for overuse, underuse, or misuse of health-care services, with well-described financial impact. In order to avoid practice variation, healthcare organizations have adopted lean methods, which were previously used in the auto industry, such as the well-known Toyota manufacturing model. Lean methods use standardized processes to obtain a final product but also remove activities that absorb resources and create no value.

Not surprisingly, our medical profession has recently seen a growing use of protocols and checklists, obtaining impressive results in terms of patient safety and practice standardization. Despite these important efforts, costs in healthcare remain a major concern. The National Health Expenditure Projections 2013-2023 estimates an annual growth rate in hospital costs of 6.2% (Centers for Medicare & Medicaid Services, http://www.cms.gov).

Therefore, many organizations moved the concept of standardization one step further and created utilization management programs. These programs use a mix of clinical, administrative, and financial methods to evaluate facility structure, standardization of processes, clinical outcomes, and resource allocation.

This integrative approach aims at optimizing quality of care, safety, and cost-containment by creating links between multiple organizational stakeholders and initiatives. (Table 1 shows the key fundamental steps for an effective Utilization Management Program.)

In 2012, a survey of directors of respiratory therapy departments administered by the American Association for Respiratory Care (AARC) showed that the vacancy rate of surveyed hospitals was only 0.81 full-time equivalents (FTEs) (Kacmarek et al. Respir Care. 2012;57[5]:710).

The calculation of FTEs for a particular department often depends on staffing models that usually assign a daily number of therapists according to the daily number of chargeable activities (also known as productivity).

Despite the common use of the aforementioned models, it has been reported that unscheduled respiratory therapist activities (patient transports, rapid response calls, etc – nonchargeable) may account for up to 40% of the daily workload. Therefore, the existent gap between actual number of FTEs and real-life RT workload may result in compromised delivery of quality care, reduction in patient satisfaction, and unsafe practices.

Utilization management programs, with involvement of respiratory therapy leadership, hospital administrators, and other institutional stakeholders, are ideal forums to address these gaps.

As an example, in an attempt to reduce overuse of RT resources and prevent eventual underuse, many organizations standardized delivery of respiratory care by switching from physician-directed treatments to RT-driven protocols. In this model, respiratory therapists use guidelines to allocate treatments according to specific clinical indications and determine the frequency of those therapies based on severity scores.

In 1998, a landmark study published by Stoller and colleagues (Am J Respir Crit Care Med. 1998;158[4]:1068) showed that the use of RT-driven protocols had greater concordance with clinical practice guidelines. Two years later, Kollef and colleagues (Chest. 2000;117[2]:467) demonstrated that similar strategies significantly reduced respiratory therapy utilization.

Our own experience, published almost 15 years later, revealed that applying an RT-driven bronchodilator strategy, rather than a physician-directed one, resulted in reduction of utilization equivalent to 0.38 FTEs (Kallam et al. Respir Care. 2013;58[3]:431).

Unpublished data from our organization showed that expanding RT-driven protocols beyond bronchodilator therapy (ie, lung-expansion therapy, bronchopulmonary hygiene, etc) may reduce costs equivalent to 1.2 FTEs.

These findings reveal that standardization of practice not only positively impacts quality of care; it also improves allocation of labor resources and alleviates staffing shortage.

Utilization management programs may be needed to address changes of multidisciplinary polices and procedures.

Institutional policies and procedures are usually regarded as rules or guidelines that determine the actions and day-to-day operations of an organization. Modification of existing policies or creation of new ones may greatly affect respiratory therapy utilization. Specifically, a recent study showed that the absence of an institutional policy in ventilator manipulation (any provider was able to manipulate ventilators) was associated with multiple changes of modes of mechanical ventilation per patient. Furthermore, each major ventilator change was associated with an increase in the odds of tracheostomy of 4.95 times and an 18.6% reduction of ventilator-free days (Modrykamien et al. Respir Care. 2015;Sept 22:abstract).

Evidently, application of new policies and procedures may have direct impact on quality of care and hospital costs.

Re-allocation of resources, reduction of costs, and improvement of quality of patient care are only a few goals of utilization management programs applied to respiratory therapy. The creation of new service lines and capital investment in new technologies may successfully be achieved if cost savings were redirected toward those goals.

In our experience, the shift in paradigm from physician-directed therapy to RT-driven protocols, associated with change in mechanical ventilator manipulation policy, allowed realignment of FTEs to a bedside bronchoscopy service line.

In conclusion, delivery of evidence-based medicine and allocation of resources are not mutually exclusive concepts. Standardization of processes of patient care, creation and modification of organizational policies, and prioritization of institutional goals may help align both objectives to provide realistic quality medicine.

Dr. Modrykamien is Clinical Associate Professor of Medicine, Health Science Center, Texas A&M University; Medical Director, Respiratory Therapy and Pulmonary Function Laboratory, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas.
Antibiotics don’t prevent poststroke pneumonia

BY MARY ANN MOON
Frontline Medical News

Prophylactic antibiotics don’t prevent poststroke pneumonia or reduce mortality, even in patients who have stroke-induced dysphagia and are at high risk of aspiration, according to a report published in the Lancet.

Routine use of antibiotics to prevent poststroke pneumonia “cannot be recommended and should be used judiciously … in patients after stroke who are managed on stroke units, even if they are at high risk of aspiration,” said Lalit Kalra, Ph.D., of the Institute of Psychiatry, Psychology, and Neuroscience at King’s College, London, and his associates.

In a prospective open-label cluster-randomized clinical trial, researchers assigned 37 stroke units in the United Kingdom to give new patients either prophylactic antibiotics for 7 days plus standard stroke care (564 patients) or standard stroke care alone (524 patients). All study participants were considered “unsafe to swallow” because they had impaired consciousness, they failed a bedside swallow test, or had a nasogastric tube.

Each hospital was allowed to choose which antibiotics to use according to their local guidelines, as well as which dosage and route of administration. The primary outcome was the incidence of post-stroke pneumonia within 2 weeks of hospitalization, which was assessed by two separate methods: a statistician masked to treatment assignment diagnosed pneumonia according to a criteria-based hierarchical algorithm, and a local treating physician diagnosed pneumonia according to clinical findings.

According to the algorithm, poststroke pneumonia developed in 13% of patients given prophylactic antibiotics and 10% of the control group, for an OR of 1.21. According to the clinical findings, poststroke pneumonia developed in 16% of the intervention group and 15% of the control group, for an OR of 1.01, the investigators said (Lancet 2015;386:1835-44).

In addition, all-cause mortality at 14 days (10%) and at 90 days (39%) was not significantly different for the two study groups. And there was no significant difference in the percentage of patients with good functional outcomes. Prophylactic antibiotics were associated with longer hospital stays than standard treatment.

Prophylactic antibiotics did reduce the number of nonpneumonia infections, especially urosepsis.

Adverse effects, including cases of Clostridium difficile-positive diarrhea and MRSA colonization, were rare and occurred in equal numbers. Prophylactic antibiotics likely “do not add to existing preventive measures such as positioning, regular suction, swallowing techniques, modified diets, and early initiation of antibiotics” if patients are suspected of developing pneumonia. Further, poststroke pneumonia is probably not just a straightforward infection but a complex respiratory syndrome.

This study was funded by the U.K. National Institute for Health Research. The researchers reported having no relevant financial disclosures.
Statins may have the unintended consequence of reducing immunotherapeutic response to and effectiveness of influenza vaccination. Potential mitigation strategies for statin-induced immunosuppression suggested by the research team include preferential use of high-dose or adjuvanted vaccines.

In a post-hoc analysis (J Infect Dis. 2013 Oct 29. doi: 10.1093/infdis/jiv456), Dr. Steven Black of Cincinnati Children’s Hospital Medical Center and colleagues derived data from an international, multisite, randomized, controlled, influenza vaccine clinical trial population of 6,961 subjects over the age of 65. At 3 weeks post vaccination, the researchers measured the level of antibodies to flu vaccine strains in the blood of statin and non–statin taking participants. Hemagglutination-inhibiting geometric mean titers to influenza A (H1N1), A (H3N2), and B strains were 38% (95% confidence interval, 27%-50%), 67% (95% CI, 54%-80%) and 38% (95% CI, 28%-50%) lower, respectively, in the statin therapy arm as compared with the non–statin therapy cohort. The effects were greater in patients on synthetic as opposed to fermentation-derived statin therapies.

In addition, a separate retrospective investigation (J Infect Dis. 2015 Oct 29. doi: 10.1093/infdis/jiv457.) tracking 137,488 patients from a Georgia managed care organization database over nine flu seasons from 2002 to 2011 also generated data implying a connection between statin use and compromised influenza vaccine efficacy and immune response.

Dr. Saad Omer of the Emory Vaccine Center at Emory University in Atlanta and his colleagues analyzed the impact of statins on influenza vaccine efficacy against medically attended acute respiratory illness (MAARI). MAARI incidence is routinely employed as influenza impact marker, although not all MAARI incidence is influenza related.

The Emory research team found that influenza vaccine effectiveness against medically attended acute respiratory illness was decreased in statin users compared with nonusers.

In EGFRm+ advanced NSCLC, NEARLY 2 OUT OF 3 cases of progression with first-generation EGFR TKIs are related to the T790M mutation.

T790M is an acquired mutation and has been identified as the most common mechanism of acquired resistance in nearly 2 out of 3 patients with advanced NSCLC.

When patients with EGFRm+ status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance, as stated in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).

Find out how the T790M mutation could affect the future of NSCLC at: EGFRevolution.com.


Influenza vaccine effectiveness against medically attended acute respiratory illness was decreased in statin users compared with nonusers.
Heroin smoking linked to early-onset emphysema

BY DEEPAK CHITNIS
Frontline Medical News
FROM CHEST

Inhalation or smoking of heroin can lead to early onset chronic obstructive pulmonary disease (COPD), according Dr. Paul P. Walker and his colleagues from the University Hospital Aintree and the University of Liverpool, England.

“We believe that we have accumulated sufficient evidence of both physiologic impairment and structural damage to identify a discrete form of early onset COPD, commonly involving emphysema, which can be attributed to inhaled opiate use,” the researchers wrote. “The widespread use of opiates as recreational drugs in some communities means that we are likely to see more obstructive lung disease in the future.”

Recreational use of opiates has been linked to asthma, but “little is known about the association between heroin inhalation and COPD beyond a study by Buster et al. [and] no previous study has examined measures of emphysema, such as detailed lung function testing or CT scan,” the researchers wrote (Chest. 2015 Nov;148(5):1156-1163).

The researchers studied 73 individuals who were aged 40 years or younger when they developed symptoms, were diagnosed with COPD, and smoked heroin regularly within the last 2 years. The mean history of smoking heroin was 14 years. The study participants additionally were regular smokers for at least 5 years, most were heavy smokers, and did not have a primary clinical diagnosis of asthma. All completed spirometry on at least one occasion when clinically stable.

Data was collected during 2005–2013, via lung function testing done when subjects were both clinically stable and a minimum of 4 weeks postexacerbation. Lung function testing was done in 12 subjects via spirometry, either prebronchodilator or postbronchodilator. High-resolution CT scans (slice thickness was no greater than 2 mm) were performed in 32 subjects each analyzed by two thoracic radiologists. Emphysema was scored on a scale of 1-5 based on guidelines produced by Sakai et al., which requires examination of a cranial level taken 1 cm above the superior margin of the aortic arch, a middle level taken 1 cm below the carina, and a caudal level taken about 3 cm above the top of the diaphragm.

Data were available from 44 of the initial 73 subjects. In the 32 who had high-resolution CT scans, their mean score — taking into account the scans of the upper, middle, and lower lung — was 2.3, indicating a 5%-25% chance of emphysema; 15 of 32 individuals had a score greater than 3, indicating a 25%-50% likelihood of emphysema, in the upper lung alone.

In the 12 subjects who underwent lung function testing, the range of the diffusing capacity of the lung for carbon monoxide was 35.5-63.0, with a median of 48 and a mean of 51. Eleven subjects had a score that qualified as “abnormal.”

Due to “lifestyle and varying motivation” not all subjects completed the investigation or returned for follow-up spirometric measurement, the researchers wrote. “Taking a history of inhaled drug use is important in patients with early-onset COPD, as is the provision of appropriate education about this new hazard of opiate use.” In some areas and populations there may be a role for case finding using spirometry.

Dr. Walker and his coauthors did not report any relevant financial disclosures.

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Important questions raised; more research required

The findings that statin use adversely affects IIV (inactivated influenza vaccine) immunogenicity and vaccine effectiveness are biologically plausible, based on known immunomodulatory effects of these drugs and raise important questions about the use of these important medications. Should these results affect a physician’s care of patients? Should statins be stopped for a period while influenza vaccine is administered? Should IIV not be administered to statin users? The answer to all of these questions is no.

Instead the results of these studies should be viewed as hypothesis generating and should prompt further investigation. If statins are found to reduce immunogenicity, then potentially transient interruption of statin therapy could be considered for testing. The effect of chronic statin use on the immunogenicity of other vaccines also needs to be evaluated further. Future studies could also evaluate whether alternative vaccination strategies with improved immunogenicity, such as high-dose, intradermally delivered, or adjuvanted vaccines will overcome the effects of statin use (if any).

The results also underscore the need for the development of influenza vaccines with improved efficacy and effectiveness.

Dr. Robert L. Atmar is a professor of medicine and interim chief of medicine-infectious disease at the Baylor College of Medicine, Houston, Texas. Dr. Wendy A. Keitel is an associate professor of molecular virology and microbiology at the Baylor College of Medicine, Houston, Texas. Dr. Atmar reported receiving grants from Takeda Vaccines. Dr. Keitel reported no relevant disclosures. Dr. Atmar and Dr. Keitel made these remarks in an editorial commentary (J Infect Dis. 2015 Oct 29. doi: 10.1093/infdis/jiv459.) that accompanied the data furnished by Dr. Black and colleagues and Dr. Omer and colleagues.
Indication
Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (e.g., fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.
Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment. The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

**Specific populations:** Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL cr 50-80 mL/min), moderate (CL cr 30-50 mL/min), or severe (CL cr less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

**You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.**

**Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.**

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.  
‡Stable was defined as no decline in lung function.

Legionellosis cases continue to increase nationwide

Core surveillance (ABCs) program on legionellosis confirm that incidences of disease caused by the bacteria are increasing across the United States, according to the Morbidity and Mortality Weekly Report (MMWR. 2015 Oct 30;64(42):1190-1193). The ABCs program, which launched in 2011, identified 1,426 cases of legionellosis over the 3-year time span, and incidence rates of 1.3 (2011), 1.1 (2012), and 1.4 (2013) cases per 100,000 individuals in the general population. This corroborates similar findings made by the National Notifiable Diseases Surveillance System (NNDSS) between 2000 and 2011, which reported an increase in the
7 Drug Interactions

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP3A, CYP1B1, and CYP2C9. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Concomitant administration of ESBRIET and fluvoxamine (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. Monitor patients closely when fluvoxamine is used at a dosage of 250 mg or more once daily.

7.2 CYP1A2 Inducers

The concomitant use of CYP1A2 inducers and ESBRIET or a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer [see Clinical Pharmacology section 12.3 in full Prescribing Information].

8 Use in Specific Populations

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (10 mg/m² body weight at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (a 1 mg/m² body weight at maternal doses of 450 mg/kg/day and higher). In a pre- and postnatal development study, prolongation of the gestation period, decreased number of live newborn, and reduced pup viability and body weights were seen in rats at oral dosage approximately 3 times the MRDD in adults (a 1 mg/m² body weight at a maternal dose of 1000 mg/kg/day).

8.2 Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (87%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration section 2.2 in full Prescribing Information].

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem such as jaundice, skin or the white of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy (see Warnings and Precautions 5.4).

Advising patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required (see Warnings and Precautions 5.3).

8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL cr  50–80 mL/min), moderate (CL, 30–50 mL/min), or severe (CL, less than 30 mL/min) renal impairment [see Clinical Pharmacology section 12.3 in full Prescribing Information]. Modify for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed (see Dosage and Administration section 2.2 in full Prescribing Information). The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information], which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

10 Overdosage

There is limited clinical experience with overdose. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4035 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation. In the event of a suspected overdose, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

17 Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling [Patient Information].

Advising patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required (see Warnings and Precautions 5.3).

8.9 Hypersensitivity Reactions

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required (see Warnings and Precautions 5.3).

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information].

Take with food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

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For further research into the disparities in legionellosis cases based on race, age, and geography, as well as the need for “more sensitive laboratory tests for legionellosis because proper diagnosis is needed for treatment and public health action.”

This study was supported by the CDC.

dctinis@frontlinemedcom.com
RSV antiviral reduces viral load, symptoms

BY MARY ANN MOON
Frontline Medical News

A n oral inhibitor of respiratory syncytial virus replication, currently called ALS-008176, significantly reduced total viral load, peak viral load, duration of viral shedding, and clinical symptoms in a small proof-of-concept study funded by the drug’s manufacturer and published online Nov. 18 in the New England Journal of Medicine.

These findings are particularly encouraging because at present, the standard of care for RSV infection is limited to supportive care only, said Dr. John P. DeVinzenzo of the departments of pediatrics, microbiology, immunology, and biochemistry, University of Tennessee, and the Children’s Foundation Research Institute at Le Bonheur Children’s Hospital, both in Memphis.

Dr. DeVinzenzo and his colleagues performed this randomized, double-blind trial during three separate study periods in which up to 22 healthy adults were confined to a special quarantine unit for 2 weeks at a time. All 62 participants were inoculated intranasally with a clinical strain of RSV and monitored twice daily for the development of RSV infection via assays of fresh nasal washings. The participants were randomly assigned to receive the first dose of ALS-008176 or a matching placebo about 12 hours after the detection of RSV, or on the morning of day 6, whichever came first.

The active drug or the placebo were administered orally every 12 hours for 5 days, for a total of 10 doses. Three dosing regimens were assessed: In the first study period, participants were given a single loading dose of 750 mg followed by nine maintenance doses of 300 mg; in the second period, participants were given a single loading dose of 750 mg followed by nine maintenance doses of 300 mg; in the third period, participants were given 10 doses of 375 mg each. A total of 35 study participants developed RSV infection.

Compared with placebo, all three dosing regimens significantly reduced viral load within 12 hours of starting treatment; by 88.0% in the first study period, by 85.3% in the second, and by 73.4% in the third. The mean interval until RSV RNA became undetectable ranged from 1.3 to 2.3 days for the three active-treatment groups, compared with 7.2 days for placebo.

RSV RNA became undetectable with-
via symptom scores and objectively
via the quantity of nasal mucus pro-
duced.

The small study population limited
the ability to detect potential safety
concerns. Nevertheless, “no serious
adverse events, premature discontin-
uation of the study drug, or clinically
significant, treatment-related adverse
events were observed in any partici-
pants in the intention-to-treat popula-
tion,” the investigators added.

They noted that people who are
infected with RSV under natural
circumstances, particularly infants,
typically present later in the course
of the disease, only after patients
or caregivers realize that the illness
is not due to a simple cold. Thus,
their disease severity would be worse
than that of these study participants
by the time ALS-008176 could be
administered. “Therefore, it may be
inappropriate to directly extrapolate
the results of this study to a clinical
setting,” Dr. DeVincenzo and his as-
sociates said.

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Visit BREOhcp.com for more information, including Patient Assistance Programs.
Shared decision making cuts unneeded antibiotics

**Shared decision making between doctors and patients for the treatment of acute respiratory infections can achieve significant short-term reductions in antibiotic use, according to a Cochrane review published Nov. 11.**

“Shared decision making is a set of communication and evidence-based practice skills that elicits patients’ expectations, clarifies any misperceptions, and discusses the best available evidence for benefits and harms of treatment,” wrote Peter Coxeter of the Centre for Research in Evidence-Based Practice at Bond University, Australia.

Dr. Coxeter and his coauthors analyzed 10 published reports from nine randomized controlled trials involving more than 1,100 physicians. The trials included nine randomized controlled trials involving 1,100 physicians.

**BRIEF SUMMARY**

**BREO** Ellipta® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

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The following is a brief summary only and is focused on the asthma indication. See full prescribing information for complete product information.

**WARNING: ASTHMA-RELATED DEATH**

Long-acting β₂-agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from nine large placebo-controlled US trials that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step-down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on medium- or medium-dose ICS (see Warnings and Precautions (5.2)).

**1 INDICATIONS AND USAGE**

1.2 Treatment of Asthma BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step-down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. See Warnings and Precautions (5.2).

**2 CONTRAINDICATIONS**

The use of BREO is contraindicated in the following conditions: Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required (see Warnings and Precautions (2.3)). Severe hypersensitivity to any component of BREO should not be used for the relief of acute symptoms or asthma exacerbations (see Warnings and Precautions (5.1), Description (11) of full prescribing information). See Warnings and Precautions (5.1). The use of BREO is not indicated for the relief of chronic bronchospasm.

**3 WARNINGS AND PRECAUTIONS**

5.1 Asthma-Related Deaths LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step-down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. See Warnings and Precautions (5.2).

**5.2 Determination of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acute deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, long-acting β₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reassessment with reassessment of the treatment regimen, giving special consideration to the possible need for escalating the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation dose of BREO daily. BREO is not recommended for the relief of chronic bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting β₂-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting β₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute exacerbation. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting β₂-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta₂-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, formoterol fumarate dihydrate) for any reason.

5.4 Local Effects of ICS in clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following infection to help reduce the risk of oropharyngeal candidiasis.

5.5 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, are more serious and can result in even fatal outcomes in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled inactivated immunoglobulin (IV Ig) may be indicated. See the respective package inserts for complete VZIG and IV Ig prescribing information. If chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, systemic fungal, viral, or bacterial infections, or active or latent tuberculosis infections.

5.6 Local Effects of ICS in clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following infection to help reduce the risk of oropharyngeal candidiasis.

5.7 Transfering Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemic active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously receiving systemic corticosteroids may need systemic corticosteroids for as long as 6 months after stopping systemic corticosteroids. Therefore, when transferring patients from systemic corticosteroids to less systemically available ICS, the details of the patient’s history should be considered, including the duration and dose of previous systemic corticosteroids usage and the underlying disease and/or prior corticosteroid treatment. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If the patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled inactivated immunoglobulin (IV Ig) may be indicated. See the respective package inserts for complete VZIG and IV Ig prescribing information. If chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, systemic fungal, viral, or bacterial infections, or active or latent tuberculosis infections.

5.8 Hypertension and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulatory system by the active effects. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong CYP3A4 inhibitor may result in HPA dysfunction (see Warnings and Precautions (5.9). Drug Interactions (7.7)). Because of the posibility of significant systemic absorption of ICS in venelous patients, patients treated with BREO should be observed carefully for evidence of systemic corticosteroid effects. Particular care should be taken in obtaining patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercortisolism and adrenal suppression (including adrenal crisis) may occur in a small number of patients to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering coadministration of BREO with long-term ketocanozole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, azoles, diltiazem).
Shared decision making ... elicits patients' expectations, and discusses the best available evidence for benefits and harms of treatment.

and 492,000 patients, and found that shared decision making interventions were associated with a 39% overall reduction in antibiotic use (95% confidence interval, 0.59-0.68) within 6 weeks of the consultation, with a trend suggesting those reductions were maintained in the longer term. The analysis also showed that this reduction did not lead to an increase in patient-initiated reconsultations or a decrease in patient satisfaction, although there were not enough data to determine the impact of these interventions on longer-term outcomes such as hospital admissions, pneumonia, or mortality (Cochrane Database Syst Rev. 2015 Nov 11. doi: 10.1002/14651858.CD010907.pub2).

Beta-adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but also reduce the risk of asthma-related deaths. The risk of death in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 16% of the population, with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. The study did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 for 12 months and with fluticasone 100 mcg in 1015 (5.1). Subjects with asthma who had a history of one or more asthma exacerbations that required treatment with oral corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age group. [See Use in Specific Populations (8.4) Asthma-related hospitalizations occurred in 4 subjects (0.7%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (0.7%) treated with BREO 100/25 (n = 131) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related hospitalizations in this trial.

Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors. Cardiovascular Disorders: tachycardia, palpitations, unstable angina. Nervous System Disorders: headache. Musculoskeletal and Connective Tissue Disorders: Muscle spasms. Renal and Urinary Disorders: Tension. Psychiatric Disorders: Nervousness. 7 DRUG INTERACTIONS 7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, nefazodone, ritonavir/indinavir, irtraconazole, telithromycin, voriconazole, itraconazole, nafoxidine, nefazodone, saquinavir, telithromycin, voriconazole, ritonavir/indinavir) (see Warnings and Precautions [5.5], Drug Interactions [7.1]). The use of such potent CYP3A4 inhibitors in combination with BREO 200/25 may reduce fluticasone furoate terminal elimination half-life, and increase fluticasone furoate systemic availability. Fluticasone furoate systemic availability is increased by 2- to 3-fold when coadministered with the strong CYP3A4 inhibitors said above (see Drug Interactions [7.1]) and ketoconazole (see Drug Interactions [7.1]). Coadministration of ketocaprene and fluticasone furoate 200 mcg once daily, and fluticasone 250 mcg once daily, and fluticasone bifronate 100 mcg twice daily in older adults with asthma. Of the 556 subjects, 29% were female and 84% were white; the mean age was 48 years. In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n = 346) or fluticasone furoate 100 mcg (n = 347) were: headache, 9% (9%); rhinitis, 7% (6%); influenza, 5% (5%); upper respiratory tract infection, 2% (2%); sinusitis, 2% (2%); and oral candidiasis, 1% (1%).
A monthly peer-led support program for adults with risk factors for heart disease achieved small but significant gains in overall cardiovascular health and smoking cessation, based on results of a multi-centered, randomized, controlled trial. After 12 months, participants scored 0.75 points higher than baseline on a novel composite measure of cardiovascular health – the Fuster-BE-WAT Score (FBS) – compared with controls, reported Emilia Gómez, Ph.D., at SHE Foundation, Barcelona, Dr. Juan Miguel Fernández-Alvira of Fundación Centro Nacional de Investigaciones Cardiovasculares, Madrid, and their associates.

Continued on following page

**Fifty-Fifty’s approach offers innovation**

The Fifty-Fifty Program offers several innovations to the field of cardiovascular prevention. First, the program did not just address one risk factor, but instead emphasized multiple aspects of cardiovascular health, including health behaviors (healthy diet and increasing physical activity) and health metrics (blood pressure, body mass index) as measured by the novel risk score, the FBS. The ability of the FBS to predict clinical outcomes has not been fully validated; but all of the included measures are intimately linked to cardiovascular health and easily reproducible in other settings, since they consist of only health behaviors and non-laboratory–based health factors.

Second, the Fifty-Fifty Program employed the widely used psychological interventions of peer support and group dynamics to yield modest yet positive results in CVH improvement at 1 year follow-up. Importantly, participants in the study selected the peer leaders. When interventions have this type of community buy-in, they are more likely to be successful. Peer-based interventions are more likely to be self-sustainable and scalable in the long term, and have wide applicability in diverse and resource-limited settings.

An important limitation of the Fifty-Fifty program was its attrition rate of 16%. Those who dropped out of the study tended to be younger and to have less favorable CVH profiles, which may have created selection bias and impacted the generalizability of the results.

Dr. Fatima Rodriguez is with the division of cardiovascular medicine, Stanford (Calif.) University. Dr. Robert Harrington is with the department of medicine, Stanford University. They reported no conflicts of interest.
Starting varenicline in the hospital cuts smoking

BY BRUCE JANCIN
Frontline Medical News

ORLANDO – Starting varenicline in smokers while they were hospitalized for an acute coronary syndrome resulted in substantially higher smoking abstinence rates than with placebo at all time points through 6 months of follow-up in the double-blind, randomized EVITA trial.

“The ACS population is typically older, they’re long-term smokers, and they come into the hospital with a life-threatening condition. Their family is all around them. They’ve had angioplasty or CABG [coronary artery bypass graft] surgery. So they have pressure on them to stop smoking. “This is a teachable moment, a window of opportunity. The public health benefit for smoking cessation in this population is huge. You can cut their risk of death and significant morbidity in half if you can get them to stop,” Dr. Mark J. Eisenberg said in presenting the EVITA results in line with numerous prior studies that have shown that less than one-third of smokers with ACS remain abstinent after leaving the hospital.

“In much the same way physicians now routinely start ACS patients on a statin, beta-blocker, and aspirin before they leave the hospital, physicians will capitalize on this opportunity to help ACS patients quit smoking as well, he said.”

“In an interview, Dr. David C. Goff, who wasn’t involved in EVITA, called the trial “a game changer” in preventive cardiology.

“The use of varenicline in ACS patients before they leave the hospital is a very important step forward. [Physicians] are increasingly comfortable with the idea of starting secondary prevention medications in the hospital, and there’s very little more that is important for a person with heart disease who smokes cigarettes than to help them quit smoking. It’s probably the No. 1 priority.”

“So evidence that we can start a medication in the hospital and get more people to quit smoking is game changing,” Dr. Goff said.

You can cut their risk of death and significant morbidity in half if you can get them to stop smoking.

DR. EISENBERG

Evidence that we can start a medication in the hospital and get more people to quit smoking is game changing.

DR. GOFF
Sacubitril/valsartan cuts heart failure readmissions

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – The combined formulation of sacubitril and valsartan cut the rate of 30-day heart failure rehospitalizations, trimming the control rate by 38% in an analysis of data from the PARADIGM-HF trial, Dr. Scott D. Solomon reported at the American Heart Association scientific sessions. This is an especially meaningful additional benefit for heart failure patients who take sacubitril/valsartan (Entresto) in place of enalapril or similar drugs because heart failure rehospitalizations have become a closely tracked metric for U.S. hospitals.

The sacubitril/valsartan combination received Food and Drug Administration approval last summer for treating chronic heart failure with reduced ejection fraction on the strength of results from PARADIGM-HF, which showed the two-drug combination substantially cut the rate of cardiovascular death and heart failure hospitalizations, compared with enalapril (N Engl J Med. 2014 Sep 11;371:993-1004).

"Chronic heart failure patients treated with sacubitril/valsartan relative to enalapril are less likely to be initially hospitalized, and subsequent to discharge are less likely to return to the hospital within 30 days, thereby reducing the risk to patients and the potential financial burden to the health care system," said Dr. Solomon, professor of medicine at Harvard Medical School and director of noninvasive cardiology at Brigham and Women’s Hospital in Boston.

This finding may help spur faster adoption of sacubitril/valsartan as the top drug for treating the renin-angiotensin-aldosterone system in heart failure patients, commented Dr. Adrian F. Hernandez, professor and heart failure specialist at Duke University in Durham, N.C. “The fact that you can derive an early clinical benefit” that becomes an early financial benefit should help counter the higher drug cost. Health care systems increasingly focus on treatments that can produce rapid benefits, both clinically and financially, said Dr. Hernandez, director of health services and outcomes research at Duke.

In fact, a cost-effectiveness analysis of sacubitril/valsartan treatment in PARADIGM-HF that included the hospital readmissions data showed that the combined formulation was "highly cost effective," compared

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Not knowing you have NTM.
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CARDIOVASCULAR DISEASE

As we continue to see findings like these, there will be [substantial] adoption of this drug.

DR. THIBODEAU

medical director of the heart failure disease management program at the University of Texas Southwestern Medical Center in Dallas. The 38% reduction in heart failure readmissions, compared with enalapril, and the 44% reduction in number of patients with a 30-day readmission was “pretty good,” she said in an interview. Plus, clinicians have already been quite excited about sacubitril/valsartan based on the primary-endpoint benefits it showed in PARADIGM-HF, “although there is always caution when a drug is brand new.”

Since U.S. marketing for sacubitril/valsartan began last summer, “there has not been a big rush to adopt it,” primarily out of the usual concerns about new agents. “As we continue to see findings like these [reduced readmissions], there will be [substantial] adoption of this drug. The new findings definitely add to its attraction,” Dr. Thibodeau said.

The two subgroups of patients who had heart failure hospitalizations in PARADIGM-HF, the 675 patients in the sacubitril/valsartan arm and the 775 in the enalapril arm, closely matched each other for virtually all demographic and clinical parameters aside from history of atrial fibrillation, which was significantly more common in the enalapril patients. Even though these two subgroups had not been randomized, the near uniform consistency of their profiles made this “a valid analysis,” Dr. Solomon said. Overall, 20% of the PARADIGM-HF patients who had a heart failure hospitalization had a rehospitalization within 30 days.

The 30-day heart failure readmission rate was 10 among patients on sacubitril/valsartan and 13% among those on enalapril, a 38% relative risk reduction that was statistically significant. The number of patients with a heart failure readmission was 44% lower in the group on the combined formulation. After 60 days, readmissions for any cause were 23% lower in the sacubitril/valsartan arm, compared with enalapril, and the combined formulation dropped the number with any 60-day readmission by 30%, he reported.

PARADIGM-HF was sponsored by Novartis, the company marketing sacubitril/valsartan (Entresto). Dr. Solomon has been a consultant to and has received research support from Novartis. Dr. Hernandez has received honoraria and research support from Novartis. Dr. Thibodeau had no financial disclosures.

Dr. Solomon, who added that he and his associates will have a full report on this in 2016.

“Not only does sacubitril/valsartan reduce mortality and hospital admissions, but it also reduced readmissions. That is very exciting. This is one of the few treatments to have this effect,” commented Dr. Jennifer Thibodeau, medical director of the heart failure disease management program at the University of Texas Southwestern Medical Center in Dallas. The 38% reduction in heart failure readmissions, compared with enalapril, and the 44% reduction in number of patients with a 30-day readmission was “pretty good,” she said in an interview. Plus, clinicians have already been quite excited about sacubitril/valsartan based on the primary-endpoint benefits it showed in PARADIGM-HF, “although there is always caution when a drug is brand new.”

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The early benefit of reduced readmissions makes it easier to justify paying a higher drug cost.

DR. HERNANDEZ

Up to 50% of all patients with bronchiectasis also have an active pulmonary NTM infection.¹

- A nontuberculous mycobacterial (NTM) lung infection is a chronic and debilitating pulmonary condition that can get progressively worse. NTM prevalence is increasing steadily, growing by 8% every year.²⁻⁵
- The signs and symptoms are common among other comorbidities, like bronchiectasis and COPD. These similarities can result in NTM being masked with patients suffering for months or years before a diagnosis.²⁻⁶
- Patients with bronchiectasis are particularly susceptible to NTM, and routine screening is recommended.¹

Think NTM? Test for NTM. Visit NTMfacts.com to learn more.
SPRINT’s results rock hypertension world

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – Results from the SPRINT hypertension trial had been highly anticipated ever since the study stopped early in August and the sponsoring National Heart, Lung, and Blood Institute released the top-line positive result in September. That finding was that treating systolic blood pressure to a target of less than 120 mm Hg led to statistically significant drops in a composite measure of cardiovascular endpoints as well as in all-cause death, compared with treating to the standard blood pressure target of less than 140 mm Hg.

When the much fuller report on the results finally came out in a special session at the American Heart Association scientific sessions as well as in a simultaneous publication (N Engl J Med. 2015 Nov 9. doi: 10.1056/NEJMoai1511939), the data left attendees buzzing and debating about what the results will mean for revised hypertension guidelines and for clinical practice.

The most prominent reactions were accolades for the trial, starting with the independent discussants that the AHA invited to comment at the session. They offered an outpouring of praise that was reminiscent of the reviews showered on a new hit movie:

“A major coup. Thank you, NHLBI,” declared Dr. Marc A. Pfeffer, professor of medicine at Harvard and a cardiologist at Brigham and Women’s Hospital in Boston.

“Thank you for this groundbreaking study,” said Dr. Clive Rosendorff, who is professor and cardiologist at Mount Sinai Hospital in New York.

“A remarkable trial. The most important blood pressure study in the last 40 years,” gushed Dr. Daniel W. Jones, who is professor of medicine at the University of Mississippi, Oxford, and the director of clinical and population sciences at the Mississippi Center for Obesity Research in Jackson.

Following the huzzahs came a more substantive discussion among meeting attendees of what the results from the 9,361-patient Systolic Blood Pressure Intervention Trial will mean for revised blood pressure goals in U.S. clinical guidelines, what it might mean for defining who has hypertension, and how it might influence practice.

Perhaps the most pressing issue for the AHA and American College of Cardiology panel that began work on a new revision of hypertension treatment guidelines earlier this year is how will the panel decide to reconcile the SPRINT results with the findings from prior studies, especially the 2010 report of results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (N Engl J Med. 2010;362[17]:1575-85).

ACCORD, at half the size of SPRINT with 4,733 patients, had a very similar study design as SPRINT but ACCORD included only patients with diabetes while SPRINT excluded patients with diabetes. ACCORD failed to show a significant difference in its primary endpoint outcome after an average of 4.7 years between patients randomized to a hypertension treatment target of less than 140 mm Hg or less than 120 mm Hg, the same goals as in SPRINT.

ACCORD did show a statistically significant 41% relative risk reduction for stroke, also in contrast to SPRINT, which showed a much less robust and nonsignificant 11% relative risk reduction in stroke.

In his commentary on SPRINT, Dr. Jones offered several possible explanations for the divergent results. Those explanations included a possible inherent difference in vascular physiology between patients with diabetes and those with normal glycemic control; the younger patients enrolled in ACCORD (patients averaged 62 years old in ACCORD and 68 years old in SPRINT, and 28% of patients in SPRINT were at least 75 years old); the use of hydrochlorothiazide as the predominant diuretic in ACCORD versus predominant use of chlorothalidone in SPRINT; and the multiple interventions simultaneously tested in ACCORD, which also randomized patients into two arms with respect to glycemic control and into two arms of different lipid-controlling treatment.

SPRINT’s results “need to be assessed in the context of ACCORD,” commented Dr. Salim Yusuf in an interview.

“I think the real result is somewhere in between the results of SPRINT and ACCORD” in terms of the appropriate systolic blood pressure target.

“What we need is a balanced perspective that takes all the trials. SPRINT was a very good trial, but like all studies it should be interpreted in the context of all the other related studies, not in isolation,” said Dr. Yusuf, professor and director of the Population Health Research Institute of McMaster University in Hamilton, Ont.

“Understandably, when something like SPRINT comes out there is a lot of enthusiasm. The first reaction is always ‘Wow!’ For patients who meet SPRINT’s enrollment criteria I think we will treat to a target of less than 120 mm Hg. But the guideline writers need to discuss SPRINT and balance it,” he said.

Despite his regard for SPRINT, Dr. Yusuf cited several additional concerns he has about the trial:

• Its early stoppage (SPRINT had originally been designed to run 5-6 years, but it was halted after an average treatment duration of just over 3 years).

“When you stop a trial early there is always an upward bias. The apparent treatment effect gets inflated,” Dr. Yusuf said.

• The increased rate of acute kidney injury among patients randomized to the more aggressive treatment arm, a 4.1% rate, compared with a 2.5% rate in the control patients randomized to treatment to a goal of systolic pressure less than 140 mm Hg, a statistically significant difference.

• The “highly selected, high-risk” patients enrolled into SPRINT. “You can’t extrapolate the results to the average patient,” Dr. Yusuf said.

Some of these concerns and cautions were shared by Dr. Prakash Deedwania, professor of medicine at the University of California, San Francisco, although overall he called the SPRINT results “very exciting.”

“Superficially, SPRINT seems to say treat everyone to a blood pressure of less than 120 mm Hg, but that’s not the case. The patients in SPRINT...”
Continued from previous page

were primarily very well established patients with hypertension.

“I’d be concerned about an elderly patient with cardiovascular disease and a blood pressure of 130 mm Hg. If you reduce that to less than 120 mm Hg the diastolic pressure may also fall and that’s important for coronary perfusion,” Dr. Deedwania observed.

He also cited the absence, so far, of a subanalysis of what happened to patients with preexisting renal disease and the lack of data on the outcomes of patients whose systolic pressure fell to levels well below 120 mm Hg.

For others, however, the overall, statistically significant 27% reduction in overall mortality was a reassuring indicator of the safety of the aggressive treatment regimen used in SPRINT.

“If there was a meaningful worsening of renal function that harmed patients, you would not see a reduction in all-cause mortality,” commented Dr. Gregg C. Fonarow, professor and associate chief of cardiology at the University of California, Los Angeles.

“We have had so many trials that couldn’t dream of producing a reduction in all-cause mortality. Here we have a trial with a robust, clinically meaningful reduction in all-cause mortality that ultimately demonstrates the benefits outweigh the risks,” he said in an interview.

SPRINT “is a phenomenal breakthrough. It’s data we’ve been awaiting for 20-plus years, to now know that a lower blood pressure target is safe and absolutely essential, and where the benefits outweigh the risks,” Dr. Fonarow said.

“Now implementation becomes critical. The SPRINT results are truly practice changing.”

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Steroids did not reduce kidney injury in CABG

SAN DIEGO – Among patients undergoing cardiac bypass surgery, perioperative use of corticosteroids did not alter the risk of acute kidney injury, results from a large randomized trial showed.

“Worldwide, over 20 million cardiac surgeries are done each year, but 4 million are complicated by acute kidney injury, and 200,000 are complicated by severe kidney injury treated with dialysis,” Dr. Amit X. Garg said during a press briefing at the annual meeting of the American Society of Nephrology. “So certainly people would benefit from a therapy to prevent acute kidney injury (AKI) and improve the safety of surgery. Dr. Garg, a nephrologist at the London Health Sciences Centre in

Continued on following page
Mixed results for mitral valve replacement vs. repair

**Continued from previous page**

Patients undergoing mitral valve replacement had a lower risk of regurgitation and heart failure–related adverse events at 2 years than those undergoing valve repair, according to the results of a trial presented at the American Heart Association scientific sessions and published simultaneously in the New England Journal of Medicine.

The trial results appear to associate mitral valve replacement with clinical advantages over mitral valve repair after 2 years of follow-up.

However, replacement held no significant advantages over repair in the primary endpoint of left ventricular end-systolic volume index (LVESVI) or in overall survival, said Dr. Daniel Goldstein, who is with the department of cardiothoracic surgery at Montefiore Medical Center, New York.

In the trial conducted by the Cardiothoracic Surgical Trials Network (CTSN), 251 patients with chronic severe ischemic mitral regurgitation were randomly assigned to undergo surgical repair of the mitral valve or to receive a mitral valve replacement with a prosthetic and procedure selected at the discretion of the surgeon.

In addition to the primary endpoint of LVESVI, the two approaches were also compared for survival, regurgitation recurrence, and heart failure events.

At 2 years, the mean change from baseline in LVESVI, a measure of remodeling, did not differ significantly between the repair and replacement arms (−9.0 vs. −6.5 mL/m², respectively).

In addition, although the 2-year mortality rate was numerically lower in the repair arm relative to the replacement arm (19% vs. 23.2%, respectively), it was also not statistically different (P = .39).

However, the rate of recurrence of moderate or severe mitral regurgitation favored replacement over repair and was significant (3.8% vs. 58.8%, respectively).

The rate of recurrence of moderate or severe mitral regurgitation favored replacement over repair and was significant (3.8% vs. 58.8%, respectively; P < .001). In addition, the rate of cardiovascular readmissions was significantly lower in the replacement group (P = .01).

For those in the repair group, there were significant trends for more severe adverse events related to heart failure (P = .05) and for a lower quality of life improvement (P = .07) on the Minnesota Living With Heart Failure questionnaire.

There were no significant differences in rates of all serious adverse events or overall readmissions.

All of the differences between groups observed at 2 years amplify differences previously reported after 12 months (N Engl J Med. 2014 Jan 2;370[1]:23-32). For example, the difference in the rate of moderate to severe regurgitation favoring replacement over repair was already significant at that time (2.3% vs. 3.6%, respectively; P < .001), even though the mortality rates were then, as now, numerically lower in the repair group versus the replacement group (14.3% vs. 17.6%, respectively; P = .45).

Dr. Goldstein reported having no financial relationships relevant to the study.

**Acute kidney injury.** Researchers are interested in corticosteroids, “because they suppress this inflammatory response. In other settings, such as acute glomerulonephritis, we successfully use corticosteroids to treat acute inflammation in the kidney,” he said.

In a study known as the Steroids in caRdiac Surgery Trial (SIRS), researchers at 79 centers in 18 countries set out to investigate if methylprednisolone alters the risk of acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass. Between June 2007 and December 2013, 7,286 patients were randomized to intravenous methylprednisolone 250 mg at anesthetic induction and 250 mg at initiation of coronary bypass, or placebo.

AKI was defined as a 0.3 mg/dL increase or greater in postoperative serum creatinine concentration from the preoperative concentration within 14 days following surgery, or a 50% increase from the preoperative value within 14 days following surgery. Secondary outcomes included different stages of AKI and receipt of acute dialysis in the 30 days following surgery. Patients, caregivers, and researchers were blinded to the treatment allocation.

Of the 7,286 patients, 3,647 received methylprednisolone and 3,639 received placebo. The mean age of patients was 60 years, 60% were men, 26% were diabetic, and 25% of patients had combined CABG and valve surgery.

When we consider the side effect profile, the most clinically relevant outcomes, and apply the GRADE framework to the evidence, we would recommend that steroids not be used in this way, with a grade 1B recommendation.

The SIRS Investigators reported that the risk of AKI was similar among patients who received methylprednisolone and those who received placebo (40.9% vs. 39.5%, respectively; relative risk 1.03). Results were similar across multiple categorical definitions of AKI, including AKI or death (41.5% vs. 40.2%; RR 1.03); AKI stage of 2 or greater (9.9% vs 9.9%; RR 1.01); AKI stage of 3 or greater (4% vs. 4.5%; RR 0.89), and being on acute dialysis (2.6% vs. 2.4%; RR 1.08).

“There was no benefit of steroids on the risk of AKI in those with or without preoperative chronic kidney disease,” Dr. Garg said. “The result was also not different in the subpopulation of patients with AKI as defined by Kidney Disease Improving Global Outcomes.”

Results from SIRS would suggest that patients undergoing cardiac surgery with cardiopulmonary bypass should not use prophylactic steroids to prevent AKI. When we consider the side effect profile, the most clinically relevant outcomes, and apply the GRADE framework to the evidence, we would recommend that steroids not be used in this way, with a grade 1B recommendation.”

The study was sponsored by the Population Health Research Institute in Hamilton, Ontario and the Canadian Institutes of Health Research. Dr. Garg reported having no relevant financial disclosures for this study.

Images: By Ted Bosworth 

Frontline Medical News
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‘Minimalist’ TAVR has short learning curve

BY RICHARD MARK KIRKNER
Frontline Medical News

A s a “minimalist” approach to transcatheter aortic valve replacement – known as MA-TAVR – gains in popularity at high-volume centers, questions persist about the surgeon’s learning curve. A small series of MA-TAVR cases at Emory University in Atlanta has shown that the learning curve may be like the TAVR approach itself: minimal.

Dr. Hanna Jensen and her associates reported on 151 consecutive patients who had MA-TAVR in the October issue of the Journal of Thoracic and Cardiovascular Surgery (J Thorac Cardiovasc Surg. 2015. doi: 10.1016/j.jtcvs.2015.07.078). They previously reported their findings at the annual meeting of the American Association for Thoracic Surgery in April in Seattle.

This study builds on an Emory study last year that reported the minimalist approach to TAVR cost about $10,000 less per patient than the standard transfemoral approach (JACC Cardiovasc Interv. 2014;7:898-904).

The operation the study authors evaluated is performed in the catheterization laboratory rather than the operating room, as in traditional TAVR. Both approaches use a femoral approach, but where traditional TAVR requires general anesthesia and transthoracic echocardiography (TEE), MA-TAVR uses local anesthesia, minimal conscious sedation, and transthoracic echocardiography (TTE).

The study authors acknowledged concerns that TTE may underestimate the severity of paravalvular leak after the procedure when compared with TEE. Their protocol relies on preoperative TTE and CT scans, or three-dimensional TEE if the case warrants it, to ensure optimal sizing of the transcatheter valve before the operation.

“If any concerns arise, our threshold is low to perform intraoperative balloon-sizing,” Dr. Jensen and her coauthors said. They also use TTE, along with a root-angiogram after valve deployment, and invasively measure the aortic regurgitation index before and after deployment.

Most study patients were high-risk surgical candidates with a median Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score of 10%. The overall major stroke rate was 3.3%, while major vascular complications occurred in 3% of patients and the greater-than-mild paravalvular leak rate was 7%.

The study retrospectively evaluated 151 consecutive patients who were divided into three groups at different time points: May 2012 to January 2013, February to August 2013, and September 2013 to July 2014. Complications were similar among all three groups, but the third group had shorter hospital stays and less time in the intensive care unit (ICU).

The first group received only the first-generation SAPIEN valve system; use of the second-generation SAPIEN XT valve increased in latter two groups. The SAPIEN XT valve is available in 23, 26, or 29 mm, but the 29-mm size was not available in the first-generation SAPIEN implant.

A subgroup analysis looked at patients who were discharged within 48 hours of the operation or more than 48 hours afterward.

The early-discharge patients had lower STS PROM scores (8.3% vs. 10.3%) and lower rates of diabetes (31% vs. 49%). They also had less need for postoperative pacemakers and less frequent rehospitalization.

“This implies that in selected MA-TAVR patients early discharge is feasible and safe, but larger studies are required to identify the optimal profile of patients who can be sent home within the first two postoperative days,” Dr. Jensen and her colleagues said.

Early in the MA-TAVR protocol all patients were sent to the ICU. As the care team gained more experience with the procedure, the protocol changed to send all patients to a regular telemetry floor after surgery unless they had vascular issues or potential need for a pacemaker.

The decreasing need for ICU “was the only indication of an institutional learning curve that was discovered, and demonstrated improved resource utilization over time,” the investigators said.

They encouraged other centers to pursue MA-TAVR. “As experience grows, we believe that this procedure can be done with less or no ICU support leading to a shorter hospital stay and improved resource utilization,” Dr. Jensen and her colleagues concluded. They called for further studies to determine the characteristics that make a patient most suitable for a short-admission MA-TAVR procedure.

Study coauthors Dr. Vasilis Babaliaros, Dr. Vinod Thourani, Amy Simone, and Patricia Keegan are research consultants with Edwards Lifesciences. The rest of the authors had no disclosures.

Hybrid revascularization: Promise, but concerns remain

BY RICHARD MARK KIRKNER
Frontline Medical News

A hybrid coronary revascularization procedure that combines off-pump left internal mammary artery (LIMA) grafting with percutaneous coronary intervention (PCI) showed good results at 1 year after surgery, but nonetheless showed a rate of adverse events that may raise questions about the procedure.

In a study published in the November issue of the Journal of Thoracic and Cardiovascular Surgery, a team of investigators from Aarhus University Hospital in Denmark reported high rates of graft patency and low rates of death and stroke with the procedure 1 year after a series of 100 operations (J Thorac Cardiovasc Surg. 2015;150:1181-6).

“The high left internal mammary artery graft patency rate and low risk of death and stroke at 1 year seem promising for the long-term outcome of this revascularization strategy,” said Dr. Ivy Susanne Modrau and colleagues.

The single-center study evaluated 1-year clinical and angiographic results of 100 consecutive trial patients with multivessel disease who had the hybrid procedure between October 2010 and February 2012.

“The rationale of hybrid coronary revascularization is to achieve the survival benefits of the LIMA to LAD (left anterior descending artery) graft with reduced invasiveness to minimize postprocedural discomfort and morbidity, in particular the risk of stroke,” Dr. Modrau and colleagues said.

The study used the LIMA to LAD graft performed off pump through a reversed J-hemisternotomy. “We chose this technique because of its excellent exposure of the heart, technical ease, low risk of complicating chronic pain, and applicability in virtually all patients,” Dr. Modrau said. Eighty-

Continued on following page
nine patients had surgery prior to PCI and 11 had PCI prior to surgery.

The primary endpoint was rate of major adverse cardiac or cerebrovascular events (MACCE), the composite of all-cause death, stroke, myocardial infarction, and repeat revascularization by PCI or coronary artery bypass grafting at 1 year. Secondary endpoints included individual components and status of stent and graft patency on angiography.

Overall, 20 patients met the 1-year primary endpoint of MACCE. One patient died, one other had a stroke, and three had heart attacks. Sixteen patients had repeat revascularization procedures, eight performed during the index hospitalization. Graft patency was 98% after 1 year.

Dr. Modrau and coauthors noted the MACCE rate of 20% “was higher than expected,” and certainly higher than results in the SYNTAX study (17.8% in the PCI group and 12.4% in the coronary artery bypass grafting [CABG] group) (Euro. Intervention. 2015;10:e1-e6).

One possible reason the Danish investigators cited for higher than expected MACCE rates was that they may be attributed to the learning curve involved with LIMA grafting and the use of early angiography possibly revealing “clinically silent LIMA graft dysfunction due to technical errors.”

The number of repeat revascularizations in the study was more in line with the SYNTAX study: 7% in the Aarhus University study and 6% in the SYNTAX CABG group.

However, a meta-analysis of six studies with 1,190 patients reported 1-year repeat revascularization rates of 3.8% after a hybrid procedure and 1.4% after CABG (Am Heart J. 2014;167:585-92).

Ultimately, the safety and efficacy of the hybrid revascularization approach will require long-term follow-up data and head-to-head comparison with conventional CABG and PCI in clinical trials. “Meanwhile, LIMA patency, the cornerstone of surgical revascularization, may be used as a surrogate endpoint for long-term survival after HCR,” Dr. Modrau and coauthors said. They reported having no disclosures.

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**VIEW ON THE NEWS**

Dr. G. Hossein Almassi, FCCP, comments: CABG remains a Class 1 indication for treatment of multivessel coronary disease, and left main coronary stenosis. As compared to PCI, CABG treats the entire coronary vessel rather than the “culprit” lesion. Hybrid coronary revascularization is reasonable in patients with one or more of the following criteria (Class Ila, Level of evidence B):

- Limitation to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI);
- Lack of suitable conduit;
- Unfavorable LAD artery for PCI (or, excessive vessel tortuosity).

This small Danish study on hybrid coronary revascularization suffers from a short follow-up time of only one year. The rate of repeat revascularization was also high. The data should be looked at carefully and one should wait for long-term outcomes.
Mild and moderate OSAS often resolves in children

BY DEEPAK CHITNIS
Frontline Medical News
FROM CHEST

Mild to moderate obstructive sleep apnea syndrome (OSAS) resolves spontaneously in many children in as few as 7 months, based on polysomnography results from the control arm of the Childhood Adenotonsillectomy Trial (CHAT).

Symptomatic improvement in snoring, however, was less common. Nonetheless, “watchful waiting may be a reasonable option in children with low OSAS symptom burden and, especially, little snoring, who also have low AHIs [apnea/hypopnea indexes] and do not have central obesity,” markers that were most likely to be associated with resolution, wrote Dr. Ronald D. Chervin of the University of Michigan, Ann Arbor.

The totality of the evidence demonstrates that OFEV slows IPF progression²⁻⁶

REPRODUCIBLE REDUCTIONS IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 TRIALS²⁻⁶

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
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<th>P-Value</th>
<th>CI 95%</th>
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<td>TOMORROW (Study 1)</td>
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• -115 mL/year for OFEV (nintedanib) compared with -240 mL/year for placebo

Gastrointestinal Disorders

Diarrhea

• Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and <1% in placebo patients, respectively.

• Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and anti-diarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting

• Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.

• If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.
Patience is rewarded

Because polysomnography is expensive, time consuming, and often unavailable, otolaryngologists will often perform an adenotonsillectomy based on a strong clinical history and parental observation in a child with snoring and chronically enlarged adenoids and tonsils. This study challenges that approach for children who have a low symptom burden, little snoring, low apnea/hypopnea indexes, and no central obesity. Admittedly, adenotonsillectomy is relatively safe, but any procedure can have complications and all have associated costs.

Dr. Ian Nathanson, of Maitland, Fla., made his comments in an accompanying editorial (Chest. 2015;148[5]:1129-1130).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

Embryofetal Toxicity: OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential hazard to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
Continued from page 40

and his colleagues. “Without surgery, habitual snoring resolves in one-half to two-thirds of affected children within 1-3 years.” The study enrolled 453 children, aged 5-9, with an AHI of at least 2 events per hour of sleep, or an obstructive apnea index (OHI) of at least 1. All children were recruited from pediatric sleep clinics and otolaryngology practices. The study did not include children with severe OSAS, which was defined as having an apnea/hypopnea index of greater than 30, an obstructive apnea index greater than 20, or oxygen saturation less than 90% for at least 2% of total sleep time. None of the study participants had recurrent tonsillitis, had a BMI z-score of at least 3, or were taking medication for attention-deficit/hyperactivity disorder, the investigators reported (Chest. 2015;148(5):1204-13). Among 453 children randomized in CHAT, 194 in the control arm had complete follow-up, remained untreated surgically, and provided data for the current analyses. Mean AHI at baseline was 6.7 (range, 1.1-29.3), mean oxygen saturation at baseline was 88.8% (range, 59%-97%), and mean score on the Pediatric Sleep Questionnaire Sleep-Related Breath-
'Without surgery, habitual snoring resolves in one-half to two-thirds of affected children within 1-3 years.'
The CHAT Study was supported by the National Institutes of Health. Dr. Cervin disclosed that he is named in or has developed, patented, and copyrighted materials owned by the University of Michigan and designed to assist with assessment or treatment of sleep disorders, including the Pediatric Sleep Questionnaire.

Sleep-Related Breathing Disorder

Scale used in this study.

He also has received support for research and education from Philips Respironics and Fisher & Paykel Healthcare, and has consulted for MC3 and Zansors.

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USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category D. [See Warnings and Precautions]. OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (in a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vascular anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., herniation, missing, or asymmetrical ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female: male ratio of approximately 71:29%) at approximately 1.5 times the MRHD in adults (in a plasma AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased postnatal viability of rat pups during the first 4 postnatal days when dams were exposed to less than the MRHD (in an AUC basis at a maternal oral dose of 15 mg/kg/day). Nursing Mothers: Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Hepatic Impairment: Nintedanib is predominantly eliminated via hepatic glucuronidation (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see Warnings and Precautions). Renal Impairment: Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²) and end-stage renal disease. Smokers: Smoking was associated with decreased exposure to OFEV which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV. OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdosage was also reported in two patients in ontology studies who were exposed to a maximum of 600 mg per day for 21 days. No serious adverse events reported were consistent with the existing safety profile of OFEV both patients recovered. In case of overdose, industrial treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Patient Information). Local Fatigue and Fatigue Fatiguing. Advise patients that they will need to undergo liver function tests and provide the public with simple materials to be used in driver’s education insurance industry to develop ways to reduce drowsy driving, educational material to be used in driver’s education and licensing examination, drowsy driving educational insurance discount programs, and technologies that mitigate against drowsy driving. In addition, AASM “encourages more research that better defines indicators of drowsy driving, identifies the threshold at which sleepiness while driving becomes dangerous, and provides the public with simple methods to determine when they might be too tired to drive safely.”

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Motor vehicle crashes involving a drowsy driver, 2009-2013

<table>
<thead>
<tr>
<th>Injury Level</th>
<th>Total Crashes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Severe injury</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Any injury</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>No injury</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>All injuries</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Any injury: Any person involved treated for injury sustained in crash.

Severe injury: At least one person admitted to the hospital.

Fatal: At least one person died within 30 days as a result of injuries.

Note: Based on data for 14,268 crashes in which a vehicle was towed from the scene.

Source: AAA Foundation for Traffic Safety
Extremes of sleep linked with early signs of CVD

BY KARI OAKES
Frontline Medical News

E xtremely short or extremely long sleep was associated with increased incidence of preclinical signs of cardiovascular disease in a large cross-sectional study of healthy and relatively young adults. Poor subjective sleep quality was also associated with early signs of CVD.

Dr. Chan-Won Kim of the Sungkyunkwan University in Seoul, South Korea, and his coinvestigators gathered self-reports of sleep quality and sleep duration from 47,109 healthy adults who underwent regularly scheduled physical examinations. Of those, 29,203 adults, 81% of whom were male, had measurements of coronary artery calcification (CAC), while 18,106 patients, 69% of whom were male, underwent brachial-ankle pulse wave velocity (baPWV) measurement. The patients were relatively young, with a mean age of 42 years for the CAC cohort and 46 for the baPWV cohort.

Coronary artery calcification and distal arterial stiffness are considered to be markers for preclinical CVD; by measuring these markers in a relatively young cohort, the investigators sought to avoid the many confounders that complicate the association between CVD and sleep in older patients with more comorbidities.

The study used multivariable analysis to control for factors such as smoking and alcohol use, marital status and education attainment, and physiologic variables including blood pressure, body mass index, and cholesterol.

Overall, more than 80% of subjects reported good subjective sleep quality, regardless of duration. However, women who reported poor sleep had a higher incidence of CAC, and men with poor sleep had a higher mean baPWV.

For sleep duration, Dr. Kim, Dr. Chang, and their colleagues found a U-shaped association between sleep duration and CAC and baPWV. Compared with individuals who slept 7 hours per night, individuals who reported sleeping less than 5 hours nightly had a CAC score ratio of 1.50, and an increase in baPWV of 9.6 cm/sec. At the other extreme, those who slept 9 or more hours per night had a CAC score ratio of 1.72 and an increase in baPWV of 6.7 cm/sec. At the other extreme, individuals who nightly had a CAC score ratio of 1.72 and an increase in baPWV of 6.7 cm/sec. At the other extreme, individuals who slept 9 or more hours per night had a CAC score ratio of 1.72 and an increase in baPWV of 6.7 cm/sec.

The results help clarify that the previously known associations between sleep duration, quality, and CVD risk are not fully attributable to the comorbidities that cause affect sleep and heart health, said Dr. Kim and associates. Though they encourage further study to delineate sleep’s contribution to CVD, their results “underscore the importance of adequate sleep quantity and quality, and support the need for considering subjects with extreme duration or poor subjective quality of sleep at risk for CVD,” they said.

In EGFRmt advanced NSCLC, NEARLY 2 OUT OF 3 CASES ARE RELATED TO THE T790M MUTATION

Lung cancer is the leading cause of cancer-related deaths both in the US and worldwide.1,4 For NSCLC EGFRmt patients, the recommended first-line treatment is EGFR tyrosine kinase inhibitors (TKIs).5

The majority of tumors will acquire EGFR TKI–resistance mutations

Despite initial high response rates with first-generation EGFR TKIs, many tumors will develop new mutations and become resistant. A major barrier to disease control is resistance to treatment. Resistance to first-generation therapy will develop in most patients with EGFRmt-advanced NSCLC on a currently approved EGFR TKI.1

After disease progression, clinical guidelines recommend subsequent treatments including either continuing with an EGFR TKI therapy or beginning platinum-based chemotherapy.1

Nearly 2 out of 3 cases of progression with first-generation EGFR TKIs are related to the T790M mutation

In patients with NSCLC who are EGFRmt, T790M is an acquired mutation and has been identified as the most common mechanism of acquired resistance in nearly 2 out of 3 patients.1,2 Development of T790M mutation may confer resistance through several potential mechanisms, which may include1:

- Steric hindrance, which reduces receptor binding of reversible EGFR TKIs
- Increased binding affinity of EGFR for ATP, resulting in reduced TKI potency

Discovering the cause of resistance

Patients should be monitored for radiologic or clinical progression. Tumors can also be assessed for molecular progression to uncover additional acquired mutations.1,3,4 When patients with EGFRmt status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance, as stated in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).5

AstraZeneca is a leader in lung cancer research

AstraZeneca is conducting ongoing research to understand the science of the T790M mutation as a driver of resistance.

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AstraZeneca is conducting ongoing research to understand the science of the T790M mutation as a driver of resistance.
On post–call day, simple cognitive skills suffer

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – If you feel sleepy and out of sorts on a post–call day, compared with a normal work–day, you’re not alone. Anesthesiology faculty reported significant increases in feeling irritable, jittery, and sleepy, along with significant decreases in feeling confident, energetic, and talkative following an on–call period, according to a study presented at the annual meeting of the American Society of Anesthesiologists.

To examine the effects of partial sleep deprivation on reaction time, simple cognitive skills, and mood status, Dr. Haleh Saadat of the Nationwide Children’s Hospital in Columbus, Ohio, and her associates obtained verbal consent from 21 anesthesiologists and measured reaction time, mood states, and eight subjective behavioral characteristics at two different time points: between 6:30 a.m. and 8 a.m. on a regular noncall day of work, and between 6:30 a.m. and 8 a.m. after an overnight call (a shift that runs from 3 p.m. to 7 a.m.). The behavioral characteristics included feeling alert, energetic, anxious, confident, irritable, jittery/nervous, sleepy, and talkative.

Reaction time decreased in all 21 subjects after night call, indicating worse performance (P = .047), while total mood disturbance was significantly higher on post–call days, relative to noncall days (P less than .001). Of the 21 anesthesiologists, 19 completed all simple cognitive task questions at both time points and reported significant increases in several of these parameters on post–call as compared with normal work days.

Post–call observations found participants feeling more irritable, and less confident and energetic, more sleepy (P less than .001), more jittery (P = .003), and less talkative (P less than .001) than on normal work days.

“Most of our subjects using problem solving, followed by seeking social support and avoidance,” Dr. Saadat noted. “People who used avoidance had greater declines in reaction time on post–call days, compared with the rest of the study participants.”

“These observations require a closer look at the potential implications for patients’ and professionals’ safety.”

The researchers reported having no financial disclosures.

dbrunk@frontlinemedcom.com
Less pneumonitis with IMRT than 3D-CRT

BY SARA FREEMAN
Frontline Medical News

SAN ANTONIO — Patients with stage II non–small-cell lung cancer undergoing chemoradiotherapy had less lung inflammation if they were treated with intensity-modulated radiation therapy (IMRT) than three-dimensional conformational radiation therapy (3D-CRT) in a secondary analysis of data from the NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0617 trial. A 44% reduction in grade 3 or higher pneumonitis cases was observed in the analysis, at 4.5% for IMRT and 8% for 3D-CRT, respectively (P = .046), Dr. Stephen Chun of the MD Anderson Cancer Center, Houston, reported at the annual scientific meeting of the American Society for Radiation Oncology.

RTOG 0617 was one of the largest studies to look at chemoradiation in patients with locally advanced non–small-cell lung cancer, Dr. Chun explained in an interview.

This phase III study examined whether there was any advantage of using high-dose (74-Gray) over standard dose (60-Gray) radiation therapy in combination with chemotherapy consisting of carboplatin and paclitaxel with or without additional cetuximab.

How the radiation therapy was delivered was left to the discretion of the treating physicians participating in the multi-institutional trial, and so the aim of the secondary analysis was to see if there was any difference in outcomes between patients who received IMRT versus those who received 3D-CRT.

“Our main hypothesis was that by using highly complex modulated beam arrangements, we would improve oncologic outcomes, whether that be toxicity or tumor control; we looked at all sorts of outcomes,” Dr. Chun said.

“We defined severe or grade 3+ pneumonitis as that requiring high steroids, oxygen, hospital admission, a ventilator, or death,” he said. “So we were really dealing with the most serious types of pneumonitis.”

Among the 482 patients studied in the analysis, 47% had received IMRT, and 53% had received 3D-RT.

“We defined severe or grade 3+ pneumonitis as that requiring high steroids, oxygen, hospital admission, a ventilator, or death,” he said. “So we were really dealing with the most serious types of pneumonitis.”

During his presentation, Dr. Chun noted that the “deck was stacked against IMRT” at baseline, with significantly more patients with stage IIIB (39% vs. 30%) and smaller mean planned target volumes (PTV, 427 mL vs. 486 mL) and a lower PTV/lung ratio (0.13 vs. 0.15) in the IMRT analysis, 47% had received IMRT, versus those who received 3D-CRT.

“With what we are seeing here, we believe that these findings support more routine use of IMRT for this population and a similar leap in lung cancer,” Dr. Chun said.

Is Skip N2 Metastasis Its Own Category?

BY RICHARD MARK KIRKNER
Frontline Medical News

So-called “skip metastasis” of lung cancer to the lymph nodes – when the cancer “skips” over the N1 bronchopulmonary or hilar stage to N2 ipsilateral mediastinal metastasis – may be associated with distinct histological characteristics that can further help understand its association with longer survival and better prognosis in advanced resectable lung adenocarcinoma, according to a small study from China.

Researchers at Fudan (Shanghai) University Cancer Center published their findings online ahead of print for the October issue of the Journal of Thoracic and Cardiovascular Surgery (205 July 6 [doi: 10.1016/j.jtcvs.2015.03.067]). In all, they enrolled 177 patients with N2 adenocarcinoma, 45 (25%) of whom had skip N2 metastasis.

They reported that patients with skip metastasis had considerably better 5-year recurrence-free survival rates of 37% vs. 5.7% and better overall survival rates of 61% vs. 32% when compared with those with non-skip involvement.

“There are distinct differences in clinicopathological features and prognosis in patients with or without skip N2 metastasis,” Dr. Haiquan Chen and his colleagues said. “Considering the results of our study, subclassifications of mediastinal lymph nodes metastases would have potential clinical significance for patients with lung adenocarcinoma.”

Dr. Chen and his colleagues sought to identify specific histological features that characterized the association between skip N2 metastasis and adenocarcinoma subtypes and prognosis. “Skip N2 patients have more cases that are acinar adenocarcinoma subtype, well differentiated and located in the right lung than [do] non-skip patients,” they said.

In fact, they found the predictive value of skip N2 was more significant in patients with right-lung disease, with 5-year recurrence-free survival of 37% vs. 0% and overall survival of 57% vs. 28% in non-right-lung lesions. Tumor size of 3 cm or smaller in skip N2 was associated with significantly improved survival rates – 43% vs. 6.7% recurrence-free survival and 75% vs. 28% for overall survival, compared with patients with larger tumors.

The skip N2 lung adenocarcinoma patients had “remarkably lower incidence” of vascular invasion of the lymph nodes, Dr. Chen and his co-authors wrote. Skip N2 patients also had lower, but not statistically significant, rates of pleural invasion. The Fudan University researchers also reported that the incidence of non-skip N2 metastasis was “significantly high” in patients with papillary-pre-dominant subtype.

“Considering our results, skip N2 should not be recognized as [a] predictor for better survival in all lung adenocarcinoma cases, but in [a] more specific group of patients,” Dr. Chen and his coauthors said. A multivariate analysis confirmed the predictive significance of skip N2 for recurrence-free survival, but not so much for overall survival. Single N2 metastasis was also an independent predictor for better recurrence-free and overall survival.

The study was funded by the Key Construction Program of the National ‘985’ Project, Ministry of Science and Technology of China; the National Natural Science Foundation of China; the Science and Technology Commission of Shanghai Municipal; and Shanghai Hospital Development Center. The authors had no disclosures.

...
SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOSTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events After Premature Discontinuation:

Premature discontinuation of oral anticoagulants, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.

- Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

- Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.

- Strong Dual Inducers of CYP3A4 and P-gp: Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
Approved for 6 indications

Treatment of PE

Reduction in risk of stroke/systemic embolism in NVAF

Treatment of DVT

Reduction in the risk of recurrent DVT and PE following initial therapy

Prophylaxis of DVT, which may lead to PE, after hip replacement surgery

Prophylaxis of DVT, which may lead to PE, after knee replacement surgery

Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT’D)

DRUG INTERACTIONS (CONT’D)

• Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

• There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.
INDICATIONS AND USAGE

Eliquis is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation—Eliquis® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery—Eliquis is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. Eliquis is indicated for the treatment of DVT. Treatment of Pulmonary Embolism—Eliquis is indicated for the treatment of PE. Reduction in the Risk of Recurrence of DVT and PE—Eliquis is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping Eliquis and prior to the intervention is not generally required. Eliquis should be restarted after the surgical or other procedures as soon as adequate heparinization has been established. (For complete Dosage and Administration section, see full Prescribing Information.)

CONTRAINDICATIONS Eliquis is contraindicated in patients with the following conditions:

• Active pathological bleeding [see Warnings and Precautions and Adverse Reactions]
• Severe hypersensitivity reaction to Eliquis (e.g., anaphylactic reactions) [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation Premature discontinuation of any oral anticoagulant, including Eliquis, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from Eliquis to warfarin in clinical trials in atrial fibrillation patients. If Eliquis is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information].

Bleeding Eliquis increases the risk of bleeding and can cause serious, potentially fatal, bleeding [see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]. Concomitant use of drugs affecting heparinization increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin antagonist/receptor antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs) [see Drug Interactions].

Advis patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue Eliquis in patients with active pathological hemorrhage. There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for Eliquis is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure [see Clinical Pharmacology (12.3) in full Prescribing Information]. Prothrombin time and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as protamine complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration [see Overdose].

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of epidural hematoma or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of Eliquis (apixaban). The next dose of Eliquis should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of Eliquis for 45 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological complication is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves. Therefore, use of Eliquis is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of Eliquis is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

• Increased risk of thrombotic events after premature discontinuation [see Warnings and Precautions]
• Bleeding [see Warnings and Precautions]
• Spinal/epidural anesthesia or puncture [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation The safety of Eliquis was evaluated in the ARISTOTLE and AVERROES studies (see Clinical Studies (14) in full Prescribing Information), including 11,284 patients exposed to Eliquis 5 mg twice daily and 602 patients exposed to Eliquis 2.5 mg twice daily. The duration of Eliquis exposure was ≥12 months for 5375 patients and ≥24 months for 3363 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (≥15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (≥3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with Eliquis and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on Eliquis and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

<table>
<thead>
<tr>
<th>Eliquis N=9088</th>
<th>Warfarin N=9052</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>327 (2.13)</td>
<td>462 (2.09)</td>
<td>0.89 (0.60, 0.80)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52 (0.33)</td>
<td>125 (0.82)</td>
<td>0.41 (0.30, 0.57)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>38 (0.24)</td>
<td>74 (0.49)</td>
<td>0.51 (0.34, 0.75)</td>
</tr>
<tr>
<td>Other ICH</td>
<td>15 (0.10)</td>
<td>51 (0.34)</td>
<td>0.29 (0.16, 0.51)</td>
</tr>
<tr>
<td>Gastrintestinal GI</td>
<td>128 (0.83)</td>
<td>141 (0.93)</td>
<td>0.89 (0.70, 1.14)</td>
</tr>
<tr>
<td>Fetal</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td>0.27 (0.13, 0.53)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>4 (0.03)</td>
<td>30 (0.20)</td>
<td>0.13 (0.05, 0.37)</td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>6 (0.04)</td>
<td>7 (0.05)</td>
<td>0.84 (0.28, 2.15)</td>
</tr>
</tbody>
</table>

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intracardiac, intra-articular, intramuscular with compartment syndrome, retroperitoneal or other significant bleeding.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid hemorrhage. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fetal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or other intracranial bleeding during the on-treatment period.

†† ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHADS2 score (a score from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).
Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ELIQUIST (apixaban)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,954</td>
<td>2,954</td>
</tr>
<tr>
<td>N (%)</td>
<td>204</td>
<td>106</td>
</tr>
<tr>
<td>N (%)</td>
<td>204</td>
<td>106</td>
</tr>
</tbody>
</table>

Table 5: Bleeding Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th>Event</th>
<th>ELIQUIST (apixaban)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>CRNM</td>
<td>25 (3.3)</td>
<td>34 (4.5)</td>
</tr>
<tr>
<td>Other</td>
<td>103 (13.1)</td>
<td>135 (17.2)</td>
</tr>
</tbody>
</table>

Table 6: Adverse Reactions Occurring in ≤1% of Patients Treated for DVT and PE in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Event</th>
<th>ELIQUIST (apixaban)</th>
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Table 7: Bleeding Results in the AMPLIFY-EXT Study

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</tr>
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</table>

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Aspartate aminotransferase increased 47 (0.9) 84 (1.2)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurred at a frequency of ≤0.1% to ≤1%.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban reduced mean apixaban AUC to 50% and 27% respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

Table 2: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extensive Treatment for DVT and PE in the AMPLIFY-EXT Study

<table>
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Table 3: Adverse Reactions Occurring in ≥1% of Patients in the AMPLIFY Study

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Table 1: Adverse Reactions Occurring in ≥1% of Patients in the AMPLIFY Study

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Table 1: Adverse Reactions Occurring in ≥1% of Patients in the AMPLIFY Study

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Table 1: Adverse Reactions Occurring in ≥1% of Patients in the AMPLIFY Study
DENVER – Genomic testing in young patients with lung cancer is critical, as the majority have adenocarcinomas harboring driver alterations that can be targeted with drugs available today, suggested a trio of cohort studies presented at a conference sponsored by the International Association for the Study of Lung Cancer.

More than three-fourths of patients aged 40 years or younger with adenocarcinoma were found to have driver alterations in genes such as those for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROSI), investigators reported in a session and related press conference.

“Lung cancer under 40 is a group of patients enriched for actionable mutations,” commented invited discussant Dr. Benjamin Levy, medical director of the thoracic oncology program for the Mount Sinai Health System in New York. “If there was ever a clinical circumstance in which next-generation sequencing should be performed routinely outside a clinical trial, it’s for these patients under 40.”

Of note, in two of the three studies, the majority of patients had some history of smoking, suggesting that this lung cancer in patients under 40 is not necessarily a non-smoking disease, he said.

New study design expands enrollment options

In the first study, a team led by Dr. Barbara J. Gitlitz, associate professor of clinical medicine at the University of Southern California in Los Angeles, analyzed data from the Genomics of Young Lung Cancer Study, the first to prospectively assess clinical characteristics and genomic alterations of this population.

The study is open to patients younger than 40 years at diagnosis. All are tested for EGFR, BRAF, HER2, KRAS, ALK, ROS1, and RET, and those negative for alterations in these genes have additional testing.

“One interesting point of our study is that people can enter either through coming to a [brick and mortar] site that has IRB approval or through a website (https://www.openmednet.org/site/alcmi-goyl) where people can remotely consent anywhere in the world and participate in our clinical trial,” Dr. Gitlitz noted.

In fact, of the 68 patients enrolled in the first year, 44% did so through the website, including some from as far away as Australia, Norway, and Turkey. The patients ranged in age from 16 to 39 years at diagnosis (median, 35 years), and 52% were female. They tended to be never-smokers, Dr. Gitlitz reported.

Lung cancer under 40 is a group of patients enriched for actionable mutations.

DR. LEVY

Fifty of the patients had stage IV adenocarcinoma at diagnosis. In this group, 76% were found to have known actionable driver alterations – most commonly in ALK (44%), EGFR (26%), or ROSI (6%). The prevalence was higher among women than men (95% vs 74%), “so there might be a different genomic spectrum of females to males,” she said. Another 14% had other driver mutations identified, most of which also were targetable. Of note, this group included a young man found to have a previously unknown EGFR kinase domain duplication who had a response to afatinib (Cancer Discov. 2015 Aug. 18. doi: 10.1158/2159-8290.CD-15-0654). “So a new, actionable EGFR mutation has been discovered through looking at young-emergent lung cancer,” noted Dr. Gitlitz.

“We hypothesized that this cohort may be a special population enriched for driver mutations, but we have far exceeded our statistical expectations, with the majority having an actionable mutation for which they are on targeted therapy, greater than 76%,” she said. “A website allowing for virtual consenting so that patients can participate remotely and use social networking to share trial information is a novel, feasible way to conduct research across continents.”

“We will continue accrual for at least another year, and my plea at this international congress is that we would very much love more international participation,” she concluded. “Ultimately, we plan a follow-up study, Epidemiology of Young Lung Cancer, to build upon our unique web-based, patient-engaged trial design.”

Most patients, 76%, had an actionable mutation for which they are on targeted therapy, Dr. Gitlitz said.

Actionable mutations are highly prevalent in young

Dr. Levy, the discussant, commented, “This study should be lauded … for taking the additional steps to look at both somatic and germline mutations via whole-exome next-generation sequencing, and also pushing the envelope for those who have no matching mutation in evaluating relevant alterations via next-generation sequencing and cell-free DNA.”

He also commended the novel web-based recruitment and consenting design, saying, “We have to put this in the context that only 5% of all lung cancer patients go on clinical trials. Anything we can do that’s novel or outside the box, as done here, is a welcome change.”

ALK translocations predominate

In the second study, Dr. Kosuke Tanaka of the department of thoracic oncology at Aichi Cancer Center Hospital in Nagoya, Japan, performed retrospective genomic screening of 67 consecutive patients who received a diagnosis of lung adenocarcinoma when aged 40 years or younger.

All patients had evaluation for EGFR and KRAS mutations, and most had evaluation for ALK translocations. Those negative for all three had additional testing.

The patients had a median age of 36 years, 60% were female, and 68% had stage IV disease, Dr. Tanaka reported. The majority, 61%, were former or current smokers.

Early-emerging adenocarcinoma has a high risk of driver oncogenes, Dr. Kosuke Tanaka said.

Overall, 82% of the patients had targetable alterations of driver oncogenes. The most common were ALK translocation (seen in 45%) and EGFR mutation (27%); KRAS mutation was uncommon (3%). Among 15 patients known to be negative for all of these, analyses identified HER2 mutations in three and RET mutations in two.

Driver mutations were more common among patients who had no or only a light smoking history, compared with peers who smoked (89% vs. 72%, P = .069). ALK translocation was more common in patients with stage IV disease (58% vs. 18%, P = .002).

“Early-emerging adenocarcinoma has a very high possibility of having some targetable driver oncogenes,” Dr. Tanaka concluded. “Among younger populations, examination of all known oncogenes, including minor ones, is strongly recommended.”

Continued on following page
Data finger genes involved in cell adhesion

In the third study, investigators performed genomic analysis in 20 patients from the Cleveland Clinic who underwent surgery for non–small-cell lung cancer (NSCLC) that was diagnosed at age 45 years or younger.

Overall, 60% were women and 65% had smoked at some time, reported lead author Dr. Patrick C. Ma of the Mary Babb Randolph Cancer Center at West Virginia University, Morgantown, and the Sun Yat-sen University Cancer Center’s State Key Laboratory of Oncology in South China and the Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

Some 55% of patients had adenocarcinomas, and 20% had stage IV disease. Of note, 25% had a history of some other type of cancer and 60% had a first-degree relative with a cancer diagnosis.

The somatic mutation rate was much higher in ever-smokers than never-smokers (3.47 vs. 0.76 per mega-base). The former value “is a relatively high mutational burden, standing shoulder to shoulder with melanoma and bladder cancer,” Dr. Ma said.

Mutations of key driver genes such as TP53 and KRAS were seen exclusively in smokers, but EGFR mutations were more often seen in never-smokers.

Genes involved in cell adhesion and epithelial-mesenchymal transition (EMT) showed a sevenfold enrichment in mutation frequency in the cohort, compared with that seen in the lung cancer data set of the Cancer Genome Atlas.

Dr. Gitlitz disclosed that she is on the speakers bureaus of Genentech and Eli Lilly. Dr. Tanaka and Dr. Ma disclosed that they had no relevant conflicts of interest.
Surgery, dose-escalated CRT yield similar outcomes

BY JENNIFER SHEPPHIRD
Frontline Medical News

After induction chemotherapy and concurrent chemoradiotherapy, patients with non-small cell lung cancer (NSCLC) who underwent surgery versus dose-escalated chemoradiotherapy had similar 5-year overall survival rates. With a median follow-up of 78 months, the 5-year overall survival for the surgery arm was 44% compared with 40% for the chemoradiotherapy arm, and progression-free survival (PFS) rates were 32% vs. 35%, respectively. In addition, the study showed no significant improvement for the surgery group in median overall survival or median PFS. Although the results did not demonstrate a benefit for surgery versus chemoradiotherapy, the 5-year overall survival data for all randomly

Important Safety Information (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

• ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing a LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformeterol tartrate, indacaterol) for any reason.

• Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.

• If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.

• Vilterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

WARNINGS AND PRECAUTIONS (cont’d)

• Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

• Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.

• Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.

• Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

• The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).

• In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umecitindium/vilterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umecitindium/vilterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.
assigned patients, “are among the best reported so far from prospective trials with definitive chemoradiotherapy,” wrote Dr. Wilfried Eberhardt, of the department of medical oncology, University Hospital Essen, Germany, and colleagues. “Both trimodality treatment that includes surgery and bimodality treatment without surgery but with a definitive chemoradiotherapy boost lead to excellent long-term [overall survival] and PFS,” the researchers wrote (J Clin Oncol 2015 Oct 26. doi:10.1200/JCO.2015.62.6812).

The multicenter phase III trial enrolled 246 patients with NSCLC stage IIIA-UICC6 (n = 75) or IIIB-UICC6 (n = 171) from 2004 to 2013. Overall, 161 patients completed induction therapy with three cycles of cisplatin and paclitaxel and concurrent chemoradiotherapy with 45 Gy, hyperfractionated-accelerated radiotherapy.

Patients who had complete, partial, or minor responses after the third cycle were assigned to surgery (n = 81) or chemoradiotherapy (n = 80). Dr. Eberhardt reported having financial relationships with Eli Lilly, Boehringer Ingelheim, Pfizer, Novartis, Roche, and several other pharmaceutical companies. Several of his coauthors reported ties to industry sources.

For patients with moderate or worse COPD
Start with ANORO ELLIPTA instead of SPIRIVA HandiHaler for superior improvement in lung function

ANORO ELLIPTA DELIVERED SIGNIFICANT IMPROVEMENT IN TROUGH FEV1 vs SPIRIVA HandiHaler AT DAY 169 IN 2 STUDIES

ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

SPIRIVA HandiHaler is an anticholinergic for the maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.

In a separate study, ANORO ELLIPTA showed a 60-mL difference* compared with SPIRIVA HandiHaler (208 mL and 149 mL, respectively), but due to testing hierarchy, statistical significance cannot be inferred.

Important Safety Information (cont’d)

DRUG INTERACTIONS (cont’d)

- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Learn more at StartWithANORO.com


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ANORO® ELLIPTA® (umecloclidium 62.5 mcg and vilanterol 25 mcg inhalation powder)
FDA approves pembrolizumab for advanced NSCLC

BY LAURA NIHOLAIDES

Prominent Medical News

The Food and Drug Administration has granted accelerated approval for pembrolizumab to treat patients with metastatic non-small cell lung cancer (NSCLC) who have disease that has progressed after other systemic treatments and tumors that express PD-L1.

The anti-PD-L1 drug is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test. Pembrolizumab was approved to treat patients with advanced melanoma in 2014. The effectiveness of the immunotherapy for treating advanced NSCLC was demonstrated among 61 patients enrolled within a larger multicenter, open-label trial.

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta₂-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umclidinium, vilanterol, or any of the excipients. See Warnings and Precautions (5.8). Description (11) of full Prescribing Information.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

• Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

• A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (3/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.

• No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.

When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient’s inhaled, short-acting beta₂-agonist becomes less effective; or the patient needs more short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta₂-Agonists

ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, iraconazole, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin, troglitazone, voriconazole) because increased cardiovascular adverse effects may occur. See Drug Interactions (7.1). Clinical Pharmacology (12.9) of full Prescribing Information.

5.5 Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator. ANORO ELLIPTA should be discontinued immediately, and alternative therapy should be instituted.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA (see Contraindications (4)).

5.7 Cardiovascular Effects

Vilanterol, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms (see Clinical Pharmacology (12.2) of full Prescribing Information). If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTC interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenergic agonist albuterol, when administered intravenous, have been reported to aggravate preexisting diabetes mellitus and hyperglycemia.

5.9 Worsening of Narrow-Angle Glaucoma

ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

5.10 Worsening of Urinary Retention

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

5.11 Hypokalemia and Hyperglycemia

Beta-agoneric agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. See Boxed Warning and Warnings and Precautions (5.1).

The following is a brief summary only; see full prescribing information for complete information in other sections:

• Paradoxical bronchospasm (see Warnings and Precautions (5.4))

• Cardiovascular effects (see Warnings and Precautions (5.7))
The anti–PD-L1 drug is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test.

* Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.9)]
* Worsening of urinary retention [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month unblinded trials (Talvia 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV1) was 48% (range: 13% to 78%), the mean post-bronchodilator FEV1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umclidinium/vilanterol 125 mcg/25 mcg, umclidinium 62.5 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n = 555) %</th>
<th>ANORO ELLIPTA (n = 842) %</th>
<th>Umclidinium 62.5 mcg (n = 418) %</th>
<th>Vilanterol 25 mcg (n = 1,034) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>&lt;1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>&gt;1</td>
<td>2</td>
<td>&gt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Neck pain</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, conivaptan, indinavir, itraconazole, levonorgestrel, midazolam, saquinavir, telithromycin, voriconazole, [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta,-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or with a history of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval should not be administered concomitantly with ANORO ELLIPTA. If concomitant use is required, patients should be monitored closely for an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce serious bronchoconstriction in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non-Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) may be accentuated by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non-potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its components, umclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ANORO ELLIPTA.

Umclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (an mcg/m2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/m2/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (in an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and mandibulocapsular Nondiabetogenic Effects: Umclidinium: There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (in an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day). Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (in a mcg/m2 basis at maternal oral doses up to 10,000 mcg/day/kg).

6.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

6.3 Nursing Mothers

ANORO ELLIPTA. It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be
Hunger hormone mimic anamorelin treats cachexia

BY NEIL OSTERWEIL
Frontline Medical News

DENVER – Anamorelin, an investigational compound that mimics the action of the so-called “hunger hormone” ghrelin, was effective at helping patients with cachexia gain weight, but fell short when it came to improving hand-grip strength, results of two clinical trials showed.

Among patients with advanced non-small cell lung cancer (NSCLC) and cachexia enrolled in two randomised trials, those who took anamorelin daily over 12 weeks gained about 1 kg of lean body mass, compared with patients on placebo, who had further losses of lean body mass.

“Weight loss and loss of appetite are dominant symptoms in lung cancer patients, especially advanced lung cancer patients. About 70% experience this problem, and it’s something we hear in the clinic every day,” said Dr. Philip Bonomi from Rush University Medical Center in Chicago.

He discussed the ROMANA 1 and ROMANA 2 trials at a briefing at a world conference on lung cancer sponsored by the International Asso-


ciation for the Study of Lung Cancer.

Cachexia, defined as a loss of 5% or more of body weight over 6 months or a body mass index below 20 kg/m2, is associated with poor clinical outcomes, including worse functional status, decreased quality of life, and shorter survival.

Anamorelin is a selective ghrelin receptor agonist that mimics the hunger-inducing and anabolic effects of the natural hormone.

In the ROMANA 1 and ROMANA 2 trials, 979 patients with unresectable stage III or IV NSCLC and cachexia were randomly assigned on a 2:1 basis to anamorelin 100 mg/day or placebo for 12 weeks. For the co-primary endpoint of change in lean body mass, patients assigned to anamorelin in ROMANA 1 (323 patients) had a median gain of 1.1 kg over 12 weeks, compared with a loss of 0.44 kg among 161 patients who received placebo (P < .001).

In ROMANA 2, the 330 patients assigned to anamorelin gained a median of 0.75 kg, while the 165 assigned to placebo lost a median of 0.96 kg (P < .001).

But for the other co-primary endpoint of improvement in hand-grip strength, there were no significant between-group differences. For the secondary endpoint of change in anorexia/cachexia in the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire, patients who received anamorelin in each trial had significantly greater mean change from baseline in scores (4.12 vs. 1.92 for placebo in ROMANA 1; P = .0004 and 3.48 vs. 1.34 in ROMANA 2; P = .0016).

exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umclidinium is excreted in human milk. However, other beta2-agonists have been detected in human milk.

8.4 Pediatric Use

There were no significant increases in either umclidinium or vilanterol exposure in children aged ≤12 years compared with exposure in healthy adults on an AUC basis).

10 OVERDOSAGE

Instruct patients to seek medical attention immediately if they experience any of the following:

• Symptoms get worse
• Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta2-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicines and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Inform patients that ANORO ELLIPTA is not meant to relieve symptoms of acute narrow-angle glaucoma.

Patients who have been taking inhaled, short-acting beta-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

Side Effects Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta2-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHD in adults on a mg/kg basis).

17 PATIENT COUNSELING INFORMATION

Inform patients that ANORO ELLIPTA is not meant to relieve symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Inform patients that ANORO ELLIPTA is not meant to relieve symptoms of acute narrow-angle glaucoma.

ANORO ELLIPTA was developed in collaboration with Theravance.

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Research Triangle Park, NC 27709

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AMR: 2R65

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Over 40% who ask for a prescription drug get it

BY RICHARD FRANKI
Frontline Medical News

About 28% of patients surveyed say that they have talked to a physician about a prescription drug they saw advertised, and 44% of those patients report that they were given the drug they asked about, according to a recent Kaiser Family Foundation Health Tracking Poll.

About 54% say that their physicians recommended behavior or lifestyle changes after being asked about a drug the patient had seen advertised, while 49% of patients say that the physician recommended a different prescription drug and 39% say that the physician recommended an over-the-counter drug, Kaiser reported.

The results were similar to those seen in a Health Tracking Poll conducted in March of 2008, when 32% of patients had talked with their physicians about a drug they had seen advertised. Of those patients, 57% had physicians who recommended lifestyle or behavior changes, 54% recommended a different prescription drug, 44% recommended the drug the patient asked about, and 30% recommended an OTC drug.

The 2015 poll was conducted by phone among a nationally representative sample of 1,203 adults living in the United States.

Dr. Michael E. Nelson, FCCP, comments: This information should make one pause and wonder who is the captain of the ship. The American Medical Association recently called for a ban on direct-to-consumer advertising from prescription drug and medical device companies. A recent market survey by Kantar Media reported that $4.5 billion was spent on drug advertising last year.

Obviously, drug advertising is effective. Dr. Benjamin Rush (1746-1813) provided advice that should be heeded today: "Do not condemn, or oppose unnecessarily, the simple prescriptions of your patients. Yield to them in matters of little consequence but maintain an inflexible authority over matters that are essential to life."

Today, this might include prescription drugs and medical devices.

When patients asked about a prescription drug they saw advertised

Note: The poll was conducted Oct. 14-20, 2015, among 1,203 adults.
Source: Kaiser Family Foundation Health Tracking Poll

VIEW ON THE NEWS

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Available January 2016

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Updates in the 2016 edition will include:
- Complex Chronic Care Services
- Examples with ICD-10-CM
- Advance Care Planning Services
- EBUS Services
- ECMO Services
- Clarification for 94640 inhalation treatments

Coding for Chest Medicine 2016 is an ideal resource for physicians, nonphysician providers, practice administrators/managers, office managers, and business managers, and this edition will contain important updates for pulmonologists, pediatricians, interventionalists, and cognitive pulmonary services.

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D

octors will have 1 more year – until Jan. 1, 2018 – to comply with Stage 3 meaningful use requirements for electronic health records (EHRs), the Centers for Medicare & Medicaid Services announced.

In its long-awaited final rule, CMS also announced simplifications to the program designed to align meaningful use with other incentive programs and shift the overall focus of the programs to make them tools for improving overall health.

The announced changes “will ease the reporting burden for providers, increase simplicity and flexibility, support interoperability and information exchange, and improve patient outcomes,” CMS Acting Principal Deputy Administrator and Chief Medical Officer Patrick Conway noted during a conference call with the media.

The final rule reduces the number of objectives from about 20 to 8 to allow doctors to find the measures that are most relevant to their practice. Measures also are better aligned, so that a single measure can allow providers to earn credit across multiple incentive programs.

CMS also explained in a separate fact sheet that it was removing many of the “check box” process measures and enhancing the focus on aspects of patient care, such as clinical decision support, e-prescribing, and information exchange.

The agency also finalized a 90-day reporting period in 2015 for all providers currently active in the meaningful use program. Given that the rule was finalized with fewer than 90 days left in the year, Dr. Conway provided additional clarity regarding the flexibility physicians will have to meet those requirements.

Those using an electronic health record on Oct. 1, 2015, “actually will not report until the end of February, and if we need to extend that time frame, we would look at that at the end of February 2016,” he said. “So, they still have almost 3 months before the reporting actually occurs.”

Dr. Conway added that even if a provider launched an EHR system after Oct. 1, “the thresholds for the program are not 100%. So, even if they were to deploy it tomorrow [and] use it successfully through the end of the year, they could then report that performance in 2016 and avoid a penalty.”

Providers also can use the exemption process if there have been implementation issues, which CMS reviews on a case-by-case basis.

Stage 2 concerns linger

There was concern that the changes did not go far enough, particularly as they relate to modifications of Stage 2 meaningful use.

“Many of the requirements for Stage 2 proved unattainable,” American College of Cardiology President Kim Allan Williams Sr. said in a statement. “Large numbers of providers either haven’t met them or, after trying and failing, have given up. That is why it is vital that CMS consider participation data from the current stage to see what is working and what isn’t before outlining an upcoming stage.”

By 2018, all providers will have to meet Stage 3 meaningful use requirements, because the earlier stages will no longer be available to help new entrants transition into the program. However, if a provider chooses to adopt the 2018 requirements a year early, they will have only a 90-day reporting requirement.

What about MACRA?

Even with the extended time line, CMS is drawing criticism for progressing with Stage 3.

“We still have some concerns about how the program is going,” Ms. Laura C. Wooster, vice president of public policy at the American Osteopathic Association, said in an interview. “One is the current meaningful use time line’s intersection with the start of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) reforms, which will replace the Medicare Sustainable Growth Rate payment system.

“Stage 3 begins voluntarily in 2017 and then is required for all physicians in 2018. MACRA begins in 2019, and electronic health record reporting will still be part of the Merit-Based Incentive Payment System.”

She expressed concern that physicians are going to have to make changes for Stage 3 meaningful use in 2018, only to have to make more changes for MACRA a year later.

UnitedHealth warns it may exit marketplace exchanges

BY JULIE APPLEBY
Kaiser Health News

Un

itedHealthGroup has laid out a litany of rea-

sons as to why it might stop selling individual health insurance through federal and state markets in 2017 – a move some see as an effort to compel the Obama administration to ease regulations and make good on promised payments.

Those problems, including low participation by healthy people, have led to financial losses, ac-

concerning with UnitedHealth. If not addressed, similar issues could affect other insurers, causing more to exit the market in the coming years, some Wall Street analysts and policy experts said.

The insurer added that it would cut its earnings forecast and projected hundreds of millions in losses stemming from the policies it sells through the health law’s marketplaces.

Stephen Hemsley, UnitedHealth chief executive officer, said too many healthy people dropped coverage and noted slower than expected enrollment.

A major factor, he added, was far higher costs for those who signed up for 2015 coverage under special exemptions after the general open-enrollment period ended. Those exemptions included, for example, people who lost their insurance, moved, or suffered a hardship, such as an eviction or had their utilities turned off. United said it did not see a similar increase in costs for people who bought policies from private brokers or websites instead of the government marketplaces after open enrollment, suggesting the reason was partly that the com-

pany’s eligibility assessments were more thorough.

The firm did not say it would halt sales in 2017 but warned that it would strongly consider doing so based on what happens in the next few months.

While seen as a serious challenge to the health care law, United’s decision alone doesn’t mark the death knell for the exchanges. In remarks to analysts and press reports, Aetna and Kaiser Per-

manente re-affirmed their commitment to selling through the marketplaces. But insurers, including Humana, Aetna, and some of the large Blue Cross Blue Shield plans, were losing money or barely breaking even on their marketplace business, ac-

concerning with earnings reports.

“If there are no changes, all the large publicly traded companies will end up leaving,” said Ana Gupte, analyst with Leerink Partners. “But I would be very surprised if [the Department of Health & Human Services] doesn’t do something to accommodate their issues.”

Those options would be limited to what the agency could do without congressional action, many analysts said. Still, that could include relaxing some regulations or reconsidering some of the exemptions that allow people to sign up after the open-enrollment period.

Former insurance executive and consultant Robert Laszewski said the administration needs to relax the rules to give insurers more flexibility to design plans that would attract healthier people.

He said the costs – including deductibles and premiums – were too high for many people, particularly those with few medical needs.

View on the News

Dr. Michael E. Nelson, FCCP, comments: While any news of a delay in the burdensome “Mean-

ingful Use” program is welcome, more welcome would be for CMS to mandate that software and hardware vendors ensure interoperability. In addition, there should be seamless collection of data that would verify meaningful use without having to mine it from one’s system.

Even more important would be the identification of the parts of the program that actually result in a positive effect in patient outcomes. Until that time, the program will only be “meaningless” for patients and a potential way for CMS to cut costs by penalizing physicians’ incomes.

The American Medical Association expressed similar concerns.

“We hope the decision by CMS to leave Stage 3 open to additional comment will allow for further improvements in the program and promote technological innovation that supports patient care,” AMA President Steven Stack said in a statement.

Given the changes that will come as a result of MACRA, CMS is taking comments on the final rule to help inform future policy on how it and MACRA will align.

gtwalktm@frontlinemedcom.com
Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

Please see brief summary of Full Prescribing Information on following pages.
INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical deterioration in patients 16 years of age and older.

Postmarketing Experience

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been formally studied in patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformations of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Summary of Controlled Trials

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than in Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo, % (n=70)</th>
<th>REVATIO 20 mg three times a day, % (n=69)</th>
<th>Placebo-Subtracted, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea exacerbated</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhage, have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after sexual activity, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal photoreceptors. Preserve REVATIO with caution in these patients.

Hearing Loss

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported to have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

DRUG INTERACTIONS

Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A4 Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than in Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)
Other drugs that reduce blood pressure Alpha blockers. In drug–drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope. Amlopidine. When sildenafil 100 mg oral was co-administered with amlopidine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic. Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 30- to 60-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis).

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (25%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardio pulmonary exercise testing in pediatric patients developmentally able to perform the test (N = 115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p = 0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment

No dose adjustment is required (including severe impairment Clcr <30 ml/min).

PATIENT COUNSELING INFORMATION

• Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

• Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

• Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

• Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only

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Higher spending, fewer malpractice claims

BY ALICIA GALLEGOS Frontline Medical News

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reater than average spending was associated with reduced risk of incurring a malpractice claim across all physician specialties in a study of almost 25,000 doctors published Nov. 4 in the BMJ. The finding is consistent with widespread beliefs that higher resource use – sometimes defined as defensive medicine – limits the risk of litigation.

Dr. Anupam B. Jena of Harvard Medical School, Boston, and colleagues compared data from the Florida Agency for Health Care Administration on all acute care hospital discharges from 2000 to 2009 with data from the Florida Office of Insurance Regulation on all closed malpractice claims against Florida physicians during the same period. The data included 24,637 physicians (pediatricians, family physicians, general surgeons, obstetrician-gynecologists, and some subspecialists), more than 18 million hospital admissions, and 4,342 malpractice claims (BMJ 2015;351:h5516. doi: 10.1136/bmj.h5516). They looked at total hospital charges associated with patients treated by a given physician in a given year, averaged across all patients treated by that physician in that year, and adjusted for patient personal and clinical characteristics.

Across all specialties, higher average spending per year was associated with a lower probability of an alleged malpractice claim in the subsequent year. Higher average spending per year was associated with reduced probability of being sued ranged from 5.7% in the bottom fifth of cesarean delivery rates to 2.7% in the top fifth. Authors note that if higher spending is motivated by concerns about malpractice, then the spending would be considered “defensively motivated.” However, that spending may not be wastefull if it is associated with fewer errors and therefore lower malpractice claims. More study is needed to compare the costs of additional resource use and the value of reduced errors to learn whether such defensively motivated care is socially wasteful or reflects socially beneficial deterrence.” The study was supported by the National Institutes of Health.

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Understanding defensive medicine

I

t may be tempting for doctors to view the results of the study by Dr. Jena and colleagues as a means to justify additional tests and procedures to mitigate the risk of a malpractice claim. We would suggest that they view the study results as a contribution to our understanding of the risk of such claims. We need to better understand defensive medicine, how to define it, how to measure it, and how its practice impacts patients and doctors.

Dr. Tara F. Bishop and Dr. Michael Pesko are with the department of health care policy and research at Weill Cornell Medical College in New York. Their comments were taken from an editorial accompanying Dr. Jena’s study (BMJ 2015;351:h5786. doi: 10.1136/bmj.h5786).
CHEST announces Dr. Barbara Phillips as its 78th President

The American College of Chest Physicians (CHEST) has announced Dr. Barbara Phillips as its new President, effective November 1. At CHEST 2015 in Montréal, the appointments of Dr. Gerard Silvestri as President-Elect and Dr. John Studdard as President-Designate were confirmed, and Dr. Curtis Sessler, who completed his term as President and became Immediate Past President of CHEST was honored.

Barbara Phillips, MD, MSPH, FCCP, is a Professor of Pulmonary, Critical Care, and Sleep Medicine in the Department of Internal Medicine, and Medical Director of the Sleep Laboratory at the University of Kentucky College of Medicine. She is board-certified in internal medicine, pulmonary medicine, and sleep medicine. After joining CHEST as an affiliate member in 1982, Dr. Phillips advanced to Fellow in 1983. She became a member of the Sleep Medicine Network and CHEST Governor of Kentucky. She has chaired the Sleep Institute and is Editor of CHEST SEEK Sleep Medicine (Second, Third, and Fourth Editions). Dr. Phillips also served for 8 years as a Regent-at-Large for the American College of Chest Physicians. Besides her work with CHEST, Dr. Phillips chaired the National Sleep Foundation and has served on the boards of the American Lung Association, the American Academy of Sleep Medicine, and the American Board of Sleep Medicine. Dr. Phillips received a Sleep Academic Award from the National Institutes of Health and was presented with the College Medalist Award at CHEST 2013. Dr. Phillips’ research interests include the effects of sleep apnea on performance and outcomes, genetic risk factors for sleep apnea, nonpharmacologic treatment of sleep apnea, and sleep in aging.

Gerard Silvestri, MD, FCCP, is the Hillenbrand Professor of Thoracic Oncology and Vice-Chair of Medicine for Faculty Development at the Medical University of South Carolina. He completed his fellowship training in pulmonary and critical care at Dartmouth. He has an advanced degree in the evaluative clinical sciences, also from Dartmouth. He is a lung cancer and interventional pulmonologist with an interest in health services research, lung cancer screening, nodule evaluation and management, and staging of lung cancer. After becoming a Fellow of the American College of Chest Physicians in 1998, Dr. Silvestri became active with the NetWorks, serving on the Steering Committees of the Thoracic Oncology and the Interventional Chest/Diagnostic Procedures NetWorks, eventually chairing the Thoracic Oncology Network. Dr. Silvestri has also served on the Nominating Committee, the CHEST Scientific Program Committee, the CHEST Foundation Development Committee, as Treasurer and Trustee on the foundation’s Board of Trustees, and as a Regent-at-Large for the American College of Chest Physicians for 3 years. At CHEST 2012, Dr. Silvestri was awarded the Pasquale Ciaglia Memorial Lecture in Interventional Medicine, and at CHEST 2014, he received the Edward C. Rosenow III, MD, Master FCCP/Master Teacher Award. Dr. Silvestri has authored more than 200 scientific articles, book chapters, and editorials, and he currently serves on the editorial board of the journal CHEST.

John Studdard, MD, FCCP, is a pulmonary and critical care physician in private practice with Jackson Pulmonary Associates in Jackson, Mississippi. Dr. Studdard completed his fellowship training at the Mayo Graduate School of Medicine. He has served in numerous CHEST leadership roles, including President and Chair of the CHEST Foundation, the philanthropic arm of CHEST; chair of the Government Relations Committee; member of the Marketing Committee; and Ex Officio member of the Diversity Committee, Scientific Program Committee, and Financial Oversight Committee. Dr. Studdard’s dedication to reducing the number of patients he treats for tobacco-related diseases, and his leadership qualities led him to serve as representative for CHEST in the negotiations with the tobacco industry leading to the Attorneys General Master Settlement Agreement of 1998. More recently, in his roles with the CHEST Foundation, Dr. Studdard served as a vice chair of the Beyond Our Walls capital campaign, the CHEST Foundation Nominating Committee, and several foundation work groups.

Curtis N. Sessler MD, FCCP, is the Orhan Muren Distinguished Professor of Medicine at Virginia Commonwealth University (VCU) Health System in the Division of Pulmonary and Critical Care Medicine, where he is Director of the Center for Adult Critical Care and Medical Director of Critical Care and the Medical Respiratory ICU. Dr. Sessler is an enthusiastic clinician and educator who has received teaching awards at VCU, including the School of Medicine Educational Innovation Award. His research interests include ICU sedation, mechanical ventilation, and infection prevention, authoring more than 300 articles, book chapters, books, and abstracts. He has served on a variety of multisociety task forces addressing research, training competency, workforce shortage, and ICU burnout. He is Past President of the Virginia Thoracic Society and has served as Chair of the Pulmonary and Allergy Drug Advisory Committee of the US FDA. An active member of CHEST, he has served on the Board of Regents and as Chair of the Critical Care Section, Chair of the Council of Sections, Chair of the Critical Care Institute, Program Chair for the 2003 CHEST annual meeting, and an Ex Officio member of the CHEST Foundation Board of Trustees. He received the Roger C. Bone Memorial Lecture award in 2010. He is a member of the editorial board of CHEST, Editor in Chief of CHEST SEEK Critical Care Medicine, and is co-section editor for Contemporary Reviews in Critical Care Medicine (in CHEST).
It’s December—the end of the calendar year and a time of reflection. When I look back on the goals we set for CHEST in 2015, I’m enthusiastic by what I see. We concentrated our efforts around the five main goals from our strategic plan to focus our work. There are many noteworthy accomplishments in each, but I’ll highlight just a few.

**Goal 1: CHEST provides the total education solution with content customized to fit individual learner needs and schedules.**

We held a very successful annual meeting in Montréal with more than 7,000 total attendees. Throughout the year, we hosted 19 live learning simulation courses in our Innovation, Simulation, and Training Center, reaching over 900 learners. With a full line of courses scheduled for 2016, we’re on track to continue providing quality education next year. People have already begun registering. Check out the calendar at chestnet.org/live-learning.

**Goal 2: CHEST has a wide array of new, relevant, and useful guidelines, standards, and complementary programs that guide the profession.**

We released eight guidelines and consensus statements in 2015. (Visit journal.publications.chestnet.org/ss/guidelines.aspx for the complete list.) And, following our model to publish updates to topics as new evidence is evaluated, we released seven chapter updates to Diagnosis and Management of Cough: Evidence-Based Clinical Practice Guidelines. Beginning January 2016, Elsevier, a world-leading provider of scientific products and services, will publish the journal CHEST, allowing us to deliver research to a larger audience and attract higher profile clinical research from around the world. I’m looking forward to seeing the impact of this new partnership.

**Goal 3: CHEST has a meaningful impact on global lung health and patient care.**

We continue to host international education events around the world. In 2015, we offered “Best of CHEST” courses in Argentina and Beijing, a board review course in Turkey, simulation training at ERS in Amsterdam, four GAIN Europe courses, and sent CHEST faculty to international education events around the globe. Through disease awareness campaigns, the CHEST Foundation is reaching both patients and clinicians. This past year, the foundation teamed up with the Foundation for Sarcoidosis Research to launch “Sarcoidosis: Seek Answers. Inspire Results” and build awareness of lung health and lung cancer at major sporting events.

**Goal 4: CHEST optimizes its assets to achieve its mission and ensure execution of its strategic plan.**

Our greatest asset is our membership. In May 2015, we updated our membership model to reflect emerging, team-based health-care models and opened membership to the entire chest medicine team. Team-based care is consistent with how health care is practiced, and it’s the way to keep advancing patient care. Under our new model, we’ve gained 90% of US chest medicine fellows-in-training as members and have maintained a 90% membership retention rate.

**Goal 5: CHEST has a strong and diverse financial base.**

I’m happy to report we had positive financial performances for CHEST, the CHEST Foundation, and CHEST Enterprises. We

Continued on following page
Societies join NAMDRC, CHEST on regulatory push; Respiratory Compromise Institute announces two projects

BY PHIL PORTE, NAMDRC EXECUTIVE DIRECTOR

NAMDRC and CHEST, along with the ATS and AARC, have submitted a series of recommendations to CMS to address an archaic, outdated Decision Memo from 2001 that stipulates that patients who receive home mechanical ventilation must have an artificial airway AND must succumb to death if the ventilator is removed. Even though the Decision Memo clearly signals that the principle of mechanical ventilation as integral to treatment, a revised policy can now be created by CMS that reflects 2013 standards of care. Importantly, the societies also emphasized that chronic respiratory failure is not always a 24/7 medical phenomenon; rather, it can occur nocturnally, intermittently, or progress into a 24/7 reality. In all of these examples, mechanical ventilation is warranted as long as respiratory failure is documented. Tangential but integral to this issue is the barrier to bilevel devices, called respiratory-assist devices (RADs) by CMS. Because the rules for access to these devices are currently so problematic, physicians understandably make the shift to ordering NIV because that is the only option available for treatment for the patient. Therefore, integral to the recommendations related to home mechanical ventilation, the societies made a series of recommendations for improvement in RAD policies, as well. These recommendations are available on the NAMDRC website at www.namdrc.org.

Respiratory Compromise Institute: The Institute is currently pursuing two specific research endeavors, and the RFP for the large, multi-year longitudinal study is open for review at both the NAMDRC website www.namdrc.org and the Institute website, www.respiratorycompromise.org. The meta-analysis is a challenge because any literature search will reveal virtually nothing with the specific term “respiratory compromise” because of its newness. The challenge, therefore, is to conduct a broad search that encompasses all the key variables in the downward cascade from respiratory insufficiency to respiratory failure to respiratory arrest. That includes literature focusing on appropriate monitoring, treatment, therapies, outcomes, length of stay, etc. The Institute hopes to award the contract at the next meeting of its Clinical Advisory Committee, scheduled for March 1. The second project focuses on Medicare data mining of hospital inpatient records. Beginning with a focus on records where respiratory failure is not present upon admission or within the first 24 hours following admission but present in the medical record, the data mining then expands outward to focus on the services provided, the length of stay, monitoring and therapies instituted, etc. A team of physician researchers are working with the data mining company to focus the research on specific ICD-9 codes (ICD-10 records will not appear in available data until late 2016/early 2017), CPT codes, and HCPCS codes. Hopefully, we will be able to begin with an initial 1 year snapshot, expanding to a multiyear longitudinal review to determine what trends, if any, exist. The data will then be sent to the physician researchers for analysis, and several papers will be generated as a result of those analyses.

NAMDRC Annual Meeting: The NAMDRC Annual Educational Conference is scheduled for March 3-5, 2016, in Palm Springs, California, at the Omni Rancho Las Palmas Resort. The entire program and registration information are available on the NAMDRC website. Registration for the conference is complimentary for new members who join NAMDRC after May 1, 2015, a value of $400. Physicians who want to take advantage of this special offer must contact the NAMDRC Executive Office at 703/752-4359.

Continued from previous page

controlled key expenses throughout the year while achieving the highest-ever revenue on the CHEST Annual Meeting, attracting higher royalties and advertising revenue, and more to improve margins. Moving into 2016, we’re financially stable because of our many valued assets. CHEST accomplished much more during 2015, and I invite you to read the details in our Advancement and Impact Report, available on chestnet.org under the “About” tab. The report recaps our accomplishments during the presidential term of Dr. Curt Sessler, FCCP, and it represents a culminating of the work of our leaders and members. CHEST has a proud history of dedicated members committed to advancing chest medicine and patient care.

Your contributions continue to make our organization a success, and I look forward to beginning another outstanding year in 2016. As always, feel free to connect with me. I invite you to follow me on Twitter (@PMarkowskiACCP), or look for me at upcoming CHEST events.
Classifieds

Professional Opportunities

Pulmonology/Intensivist
Join eight university trained, Board Certified Pulmonary, Critical Care and Sleep Medicine physicians. Our integrated multi-specialty physician clinic and hospital includes a Level II Trauma Center and an accredited sleep center. Practice with strong colleagues in the region’s tertiary referral center.

Physician-Led Medicine in Montana
Billing Clinic is nationally recognized for clinical excellence and is a proud member of the Mayo Clinic Care Network. Located in the magnificent Rocky Mountains in Billings, Montana, this friendly college community has great schools, safe neighborhoods and family activities. Exciting outdoor recreation minutes from home. 300 days of sunshine!

Contact: Rochelle Woods
1-888-554-5922
physicianrecruiter@billingsclinic.org

Billings Clinic

Inpatient Pulmonary/Critical Care Position in Maine:
Join a vibrant Inpatient Pulmonary and Critical Care group of five in beautiful Maine! Central Maine Medical Center (CMMC) is seeking a BC/BE Pulmonary/Critical Care Physician to help provide pulmonary and critical care services to medical, surgical, trauma, and cardiac patients.

CMMC is a 250 bed, full service regional referral center with busy trauma, cardiologyc, interventional radiology, vascular, and neurosurgical programs. We have a state-of-the-art 15 bed ICU and a separate 15 bed cardiologyc unit.

Competitive salary and benefits including CME, paid vacation, student loan repayment, 403b match, and relocation fees. Work schedule revolves around 6 day on and 6 day off philosophy, with no longer than 12 hour shifts per day. There is no outpatient clinic work.

Residents and visitors enjoy an extraordinary lifestyle that revolves around top school systems, ski resorts, lake and ocean water sports, theatre, and world-class dining.

Interested applicants may submit CV to Julie Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: jlauver@cmmc.org, Fax: 207/795-5696. Call: 800/446-7431. Visit our website, www.cmmc.org.

Memorial Cardiac and Vascular Institute

Cardiac Intensivist Employment Opportunity

Memorial Healthcare System is seeking a critical care physician, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate clinical skills, a broad knowledge base in critical care and dedication to providing high quality, evidence-based care. Applicants must be BE/BC in critical care medicine. Previous experience in managing cardiac surgery patients is a plus but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

- 12-hour in-house shifts (7 pm-7 am); no responsibilities outside of in-house shifts
- Approximately 15 shifts per month (more if desired)
- Highly competitive salary differential for the nocturnist position

This is a full-time employed position within the multispecialty Memorial Physician Group. The position offers competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

About Memorial Healthcare System

Memorial Healthcare System is the third-largest public healthcare system in the United States. A national leader in quality care and patient satisfaction, Memorial has ranked 11 times since 2008 on nationally recognized lists of great places to work -- in Modern Healthcare magazine, Florida Trend magazine and Becker's Hospital Review, just to name a few.

Memorial’s facilities include its flagship, Memorial Regional Hospital, one of the largest in Florida; Memorial Regional Hospital South; Joe DiMaggio Children’s Hospital, the only freestanding children’s hospital in Broward and Palm Beach counties; Memorial Hospital West; Memorial Hospital Miramar; Memorial Hospital Pembroke; and Memorial Manor, a US News five-star-rated nursing home.

Memorial’s work environment has been ranked by employees and physicians alike as an open-door, inclusive culture that is committed to safety, transparency and, above all, outstanding service to patients and families.

memorialphysician.com

Disclaimer

Chest Physician assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.
Mount Nittany Health Pulmonologist Opportunity

Position Highlights include:
- Mount Nittany Physician Group currently provides a range of pulmonary medicine services including interventional procedures, allergy/immunology, and sleep medicine.
- Established practice with 6 physicians and growing patient demand within an expanding health system
- Mix of outpatient pulmonary medicine/procedures and inpatient pulmonary consults.
- Fully integrated EMR, electronic documentation and order entry
- Limited intensivist work available if desired, not required

Mount Nittany Medical Center, located in State College, PA, is a not-for-profit, 260 bed, acute care facility housing both inpatient and outpatient medical/surgical services. It is a growing and thriving facility offering unparalleled patient-focused care made all the more distinctive by excellent physicians, ease of access and facilities and systems engineered for the best in patient care.

State College, home to Penn State University, is a vibrant college town. It offers a diverse culture, a beautiful environment, excellent public and private schools, countless options for dining, theatre, sports and recreation, nightlife and more. This is all located within a safe, friendly community that makes the area perfect for raising a family. University Park Airport is located only five miles from town and State College offers easy access to Internates 80 and 99.

Shefy Palumbo
Physician Recruiter
State College, PA
(814)231-4392 or (814)568-6223
michele.palumbo@mountnittany.org
www.mountnittany.org

WISCONSIN

Ministry Health Care
PULMONOLOGY /CRITICAL CARE OPPORTUNITY
UPPER MIDWEST

Ministry Health Care is actively seeking a BC/BE Pulmonology/Critical Care physician for a growing program at our 119-bed tertiary referral center in Weston, WI. This is an excellent opportunity to join a financially sound, physician-led organization, treat a broad scope of cases and play a significant role in the growth and success of our program.

- Call is 1:4
- 12+ ICU bed coverage with significant support from Hospitalist team, Anesthesia and E-ICU
- EBUS and EUS on site; would support any procedures you are interested in
- Strong, established referral network
- Digitally advanced facility consistently named one of the nation’s “Most Wired” hospitals

You’ll enjoy an excellent quality of life in the Wausau/Weston area. The community is vibrant, safe and affordable and offers a full complement of metropolitan amenities complete with a downhill ski resort and a regional airport.

CONTACT: BRENDAS CHAMBERS (715) 342-6579
mmgreecruitment@ministryhealth.org
www.ministryhealth.org

PRESBYTERIAN

PULMONOLOGY / CRITICAL CARE PHYSICIAN

Presbyterian Healthcare Services (PHS) is seeking a Pulmonary/Critical Care trained physician to join our established group.

The physician will consist of 75% Critical Care and 25% Pulmonary.

PHS is a non-profit integrated health care system that employs over 600 providers and includes a healthplan.

Benefits include medical, dental, vision, 403(b) plus match, CME, malpractice coverage (tail insurance included), competitive salary, sign on bonus and relocation assistance.

For more information, please contact:
Kelly Herrera
505-973-5662
kherrera@phs.org

MEMORIAL HEALTHCARE

Critical Care Medicine Employment Opportunity

Join a Leading Healthcare System in South Florida

Memorial Healthcare System is seeking an Intensivist, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base and dedication to providing high quality, evidence-based patient care. Applicants must be BE/BC in critical care medicine. Currently, the critical care program includes 28 full-time intensivists and six critical care ARNPs. The successful candidate will integrate into the existing operational structure, joining the team of eight dedicated full-time nocturnists.

- 12-hour in-house shifts (7 pm – 7 am); no responsibilities outside of in-house shifts
- Approximately 12 – 14 shifts per month (more if desired)
- Highly competitive salary differential for the nocturnist position

This is a full-time employed position within the multispecialty Memorial Physician Group. The position offers competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

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Join us at CHEST World Congress 2016

April 15 – 17, 2016
Shanghai, China, will set a perfect backdrop for CHEST World Congress 2016. This unique, modern city will keep you moving and thinking, as we make sure you’re informed on the latest updates and innovations in chest medicine.

CHEST, in collaboration with the Chinese Thoracic Society, will host this clinical event, featuring simulation-based education, case- and problem-based sessions, and evidence-based medicine for clinical respiratoryists, intensive care physicians, and specialists in sleep medicine.

On Friday, April 15, we’ll offer postgraduate courses for an intensive learning experience. With additional registration, you can choose from the following topics:

• Advanced Mechanical Ventilation
• Clinical Pulmonary Medicine: A Case-Based Review
• Lung Cancer Education Program: A Multi-disciplinary Team-Based Approach
• Thoracic Ultrasoundography for the Pulmonary and Critical Care Consultant

We’ll also enhance your skills in a hands-on clinical environment within our CHEST Simulation Center. Work with expert faculty to sharpen your skills and apply your knowledge using real equipment and simulators. With additional registration, you’ll choose from the following topics:

• Ultrasonography for the Assessment of Cardiopulmonary Failure
• Bronchoscopy Procedures: EBUS-TBNA, Radial EBUS, and Endobronchial Blockers
• Mechanical Ventilation: Techniques to Optimize Care of the Critically Ill Patient
• Home-Based Sleep Apnea Testing
• Advanced Positive Airway Pressure Devices and Downloads
• Pulmonary Function Testing: A Case-Based, Hands-On, Guidelines-Driven Practicum

When you have some free time, be sure to explore Shanghai. You will be immersed in a wonderful Chinese culture, complete with flavorful, authentic food; exquisite, local architecture and gardens; and a native language with beautifully written characters.

Learn more and register today at chest-worldcongress2016.org/.

This Month in CHEST

Editor’s Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP
Editor in Chief, CHEST

Pulmonologists’ Report-Ed Use of Guidelines and Shared Decision-making in Evaluation of Pulmonary Nodules: A Qualitative Study. By Dr. R. Soylemez Weiner et al.

Primary Care Providers and a System Problem: A Qualitative Study of Clinicians Caring for Patients With Incidental Pulmonary Nodules. By Dr. S. E. Golden et al.

Management of Pulmonary Nodules by Community Pulmonologists: A Multicenter Observational Study. By Dr. N. T. Tanner et al.

Lung-Dominant Connective Tissue Disease: Clinical, Radiologic, and Histologic Features. By Dr. N. Omote et al.

The Use of a Fully Automated Automatic Servoventilation Algorithm in the Acute and Long-term Treatment of Central Sleep Apnea. By Dr. S. Javaheri et al.
PQRS reporting: Do you understand your risk?

Do you understand your PQRS financial risk?
Successful reporting doesn’t just satisfy 2015 reporting requirements but will also help you to avoid fast approaching PQRS and Value-Based Modifier penalties.

Value Modifier Penalty for 2015 PQRS Nonreporters
- Groups with 2-9 Eligible Professionals (EPs) and solo practitioners: automatic -2.0% of Medicare Physician Fee Schedule (MPFS) downward adjustment
- Groups with 10+ EPs: Automatic -4.0% of MPFS downward adjustment

Quality-Tiering for Successful 2015 PQRS Reporters
- Groups with 2-9 EPs and solo practitioners: Upward or neutral value modifier adjustment only based on quality-tiering (+0.0% to +2.0x of MPFS)
- Groups with 10+ EPs: Upward, neutral, or downward value modifier adjustment based on quality-tiering (up to -4.0% to or +4.0x of MPFS)

Eligible professionals have several options to participate in annual PQRS reporting to avoid PQRS and VBM automatic penalties, including Measures Groups, Individual Measures, and Group Practice Reporting Option (GPRO) reporting for practices reporting through the GPRO.

Don’t know where to begin? The PQRSwizard, a CHEST-affiliated product, can help.

The PQRSwizard is a fast, convenient, and cost-effective online tool to help collect and report quality measure data for the CMS PQRS incentive payment program.

Don’t know where to begin? The PQRSwizard helps guide you through a few easy steps to help rapidly collect, validate, report, and submit the results to CMS for payment.

Learn more about PQRSwizard during a live demo on December 7 at 2:00 PM ET or on January 19 at 12:00 PM ET. CE City’s PQRS experts will provide a guided tour of reporting using the PQRSwizard.

Register for the webinar by going to acquire.pqrswizard.com and clicking on “View webcasts.”

<table>
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<th>Physician group size</th>
<th>Reporting year</th>
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<th>Providers/groups that DO successfully report PQRS</th>
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<td>PQRS</td>
<td>Value-based modifier adjustment</td>
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<td>2015</td>
<td>2017</td>
<td>-4% (includes PQRS &amp; VBM penalties)</td>
<td>No penalty Neutral (0%) Upward (up to 2%)</td>
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<tr>
<td>10+</td>
<td>2015</td>
<td>2017</td>
<td>-6% (includes PQRS &amp; VBM penalties)</td>
<td>No penalty Negative (up to –4%) Neutral (0%) Upward (up to 4%)</td>
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Table 1. Summary of financial risk for the 2015 PQRS and VBM programs by practice size.
ABIM continues to offer MOC benefits for newly certified Internal Medicine physicians and fellows

BY DR. KEVIN M. CHAN, FCCP, DR. SERPIL C. ERZURUM, FCCP, AND DR. PETER H.S. SPORN, FCCP, for the ABIM Pulmonary Disease Board

If you are an American Board of Internal Medicine (ABIM) Board-Certified physician newly certified in Internal Medicine, or a fellow who has completed an accredited fellowship year, ABIM recognizes the work that goes into those efforts with fee waivers, credits, and MOC points. When ABIM updated its MOC program in January 2014, the program was designed to provide continuous learning opportunities for doctors and to help physicians, their colleagues, and their patients know that they were staying current in knowledge and practice throughout their careers.

Recognizing that those who have just completed training and those engaged in fellowship are just beginning their careers or are embedded in learning environments, ABIM wants to recognize this work as part of MOC and, thus, not burden these individuals with additional MOC costs or activities.

For those newly certified in Internal Medicine:
• Passing the Internal Medicine exam earns a waiver that covers the MOC program fee for the first calendar year after earning the certification.
• A diplomate will need to enroll in MOC but will not owe any fees of successfully completed accredited fellowship training.

It’s important to note that the fee credit is not automatically applied to a diplomate’s account; rather, every year a credit is earned, it must be claimed when enrolling in MOC via the Physician Login.

Fellows and recent graduates are encouraged to confirm with their program director that evaluations have been submitted (via ABIM’s online clinical competence evaluation system (FasTrack®)) following a year was completed (Most often training years end in June, but this may vary for some academic years at some institutions).

Please note: fellows and recent graduates (within 5 years of completing an initial certification examination in Internal Medicine or a subspecialty) will remain certified whether or not they choose to enroll in MOC.

However, if they participate in an unaccredited training year either before or after accredited training years, they may need to pay an MOC program fee for that year in order to be reported as participating in MOC, since fee credits are granted for the calendar year after successful completion of accredited training years (most academic years end in June).

Unaccredited years may include:
• year(s) spent working as a hospitalist between residency and fellowship,
• research years that are unaccredited, and
• a year as a chief resident, usually occurring immediately following residency before starting fellowship.

However, as noted above, if fellows do not enroll in MOC and pay the MOC program fee for the calendar year after the unaccredited training year, they will remain certified as long as they are meeting all other programmatic requirements, but will be reported as not participating in MOC.

Fellows will be reported as participating in MOC as soon as they enroll in the MOC program by either paying the MOC program fee or claiming the fee credit earned through fellowship training.

Going forward, as they successfully complete accredited training years, fellows will receive the fee credit that can be applied to the MOC program fee due each subsequent calendar year.

*Fellowship years in ABIM subspecialties completed in 2014 and after are eligible if accredited by the Accreditation Council for Graduate Medical Education (ACGME), the Royal College of Physicians and Surgeons of Canada, or the Professional Corporation of Physicians of Quebec.

Currently, only accredited years are tracked by ABIM in its online clinical competence evaluation system, and, therefore, only the accredited years can be verified reliably across all programs for satisfactory completion.

In doubt, fellows should contact their program directors to verify whether their training is accredited.

We encourage you to visit and subscribe to the Transforming ABIM blog (http://transforming.abim.org) to learn more about ABIM’s ongoing discussions regarding certification and MOC, as well as upcoming opportunities to provide input.

To learn more about your specific requirements and deadlines, or to check your certification status, log into www.abim.org to view your MOC Status Report.

We look forward to sharing updates as we work to ensure the relevancy of MOC to pulmonary disease physicians.
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